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**Total Pancreatectomy and Autologous Islet
Transplantation for Chronic Pancreatitis**

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Introduction

Chronic pancreatitis is characterized by progressive inflammation and parenchymal fibrosis, leading to irreversible morphologic changes, including ductal calcifications, strictures, and pseudocyst formation, as well as permanent loss of exocrine and, eventually, endocrine function. The most common associated risk factor is alcohol consumption, although the importance of genetic/hereditary factors has been increasingly recognized. Exocrine dysfunction (which is experienced by patients as steatorrhea, malabsorption and malnutrition) can be managed by pancreatic enzyme replacement therapy. Clinically relevant endocrine dysfunction is usually not apparent until the later stages of disease and is managed by exogenous insulin. Clinically, the most troubling symptom is pain, which may be severe and unrelenting or only episodic. It is the symptom of pain that most negatively impacts quality of life, and leads to significant disability including loss of employment, substance dependence, and social stigmatization. The management of pain remains challenging. Its severity does not always correlate with the extent of morphologic changes identified on imaging studies. Many patients become dependent on narcotic pain medications.

Surgical intervention for chronic pancreatitis may be indicated for patients with incapacitating pain that is refractory to medical management. There are a variety of operations that have been described for the treatment of chronic pancreatitis, which are detailed elsewhere in this text. The choice of operation largely depends on anatomical considerations and the presumed mechanism of pain. For example, for patients with large-duct disease in whom the mechanism of pain may be related to ductal obstruction, a decompressive procedure such as lateral pancreaticojejunostomy may be indicated. On the

other hand, a partial pancreatic resection may be indicated for patients with a dominant inflammatory mass.

However, some patients with chronic pancreatitis or recurrent acute pancreatitis have no conventional surgical option, due to lack of a suitable anatomic target (i.e. small duct disease, diffuse disease). Others have persistent or recurrent pain despite operative intervention. For this subset of patients, total pancreatectomy with islet autotransplantation (TP-IAT) may be a reasonable option (Figure 1).

Indications and patient selection

Total pancreatectomy (TP) for malignant disease of the pancreas was first described in 1943 by Rockey. In the 1960s, a small series of TP for patients suffering from the intractable pain of chronic pancreatitis began to appear in literature. Although significant pain relief was reported in majority of the patients, it was generally reserved for the most exceptional clinical circumstances in the late stages of disease, due to considerable morbidity associated with the procedure. TP removes diseased pancreatic parenchyma, but also leads to the complete loss of islet cells. This results in brittle insulin dependent pancreatogenic diabetes (Type 3c). Glycemic control after TP is challenging due to loss of glucagon-dependent counter-regulation, leading to frequent episodes of hypoglycemia and/or ketoacidosis. In addition, complete exocrine insufficiency after TP requires high dose pancreatic enzyme supplementation.

To preserve islet cell function, Sutherland and colleagues from University of Minnesota performed the first islet autotransplantation (IAT) in 1977. Since then, with advances in surgical techniques and improvements in islet cell preparation, a number of

specialized centers have developed programs to treat chronic pancreatitis patients by combining total, completion, or near-total pancreatectomy with IAT.

An expert panel from Pancreas Fest held in Pittsburgh in 2012 concluded that TP-IAT is an effective treatment option for highly selected patients with severe painful chronic or recurrent acute pancreatitis. There was consensus that the primary indication for the procedure was intractable pain despite other treatment modalities and not amenable to conventional alternatives. Detailed patient selection criteria for TP-IAT have been proposed by the University of Minnesota group (Table 1) and have generally been adopted by most institutions. However, morphologic changes in the pancreas such as atrophy or fibrosis can be caused by aging, alcohol intake or diabetes. Also, chronic narcotic use may result in opioid hyperalgesia (OH) and narcotic bowel syndrome, which makes it difficult to differentiate pancreatitis from other sources of abdominal pain. Therefore, patient selection of patients for TP-IAT remains challenging. TP-IAT should be performed only after extensive discussion between the patient and the providers in multi-disciplinary setting.

The patients who suffer from certain forms of genetically-linked chronic pancreatitis deserve special consideration for TP-IAT. Gene mutations in the cationic trypsinogen (PRSS1) gene, the cystic fibrosis transmembrane conductance regulator (CFTR) and serine protease inhibitor Kazal type 1 (SPINK1), all predispose carriers to recurrent acute and chronic pancreatitis. In particular, for patients with hereditary pancreatitis associated with PRSS1 gene mutation, the lifetime risk of pancreatic cancer is approximately 40%, which represents a 25-fold increased risk compared to smoking. Therefore, a lower threshold for TP-IAT may be reasonable in this patient population. It is important to note, however, that TP-IAT has not been formally studied as a method to reduce cancer risk. However, no

pancreatic cancer has been reported in the post-TP-IAT setting since its introduction nearly 40 years ago.

There are several contraindications for TP-IAT. TP-IAT should not be performed in patients with active alcoholism, active illicit drug use or uncontrolled psychiatric illness that could impair compliance with complex medical management. In addition, TP-IAT should not be performed in patients with C-peptide negative diabetes, Type 1 diabetes, portal vein thrombosis, portal hypertension, end-stage liver disease, or high-risk cardiopulmonary disease. There are case reports of TP-IAT being utilized in the setting of malignancy, including our own report. However, due to risk of contamination of the islet prep with tumor cells and possible dissemination of malignancy, this approach is controversial and is currently not recommended.

Surgical Technique

Total Pancreatectomy

The surgical approach to total pancreatectomy varies among high volume TP-IAT centers, as summarized in Figure 2. One common feature, however, is the effort to preserve the blood supply of the pancreas as long as possible, to minimize the warm ischemia time for the islet cells. To achieve this, the gastroduodenal artery and the splenic artery and vein are preserved until just prior to resection. This is a crucial element of TP for IAT, since islet yield directly correlates with graft success rate in multiple studies.

In some centers, pancreatectomy is performed without transection of the pancreas to keep the pancreatic capsule intact and facilitate collagenase digestion of the parenchyma. However, others, including our group, feel that this prolongs the procedure and potentially

increases the ischemia time. Therefore, we usually divide the parenchyma at the neck of the pancreas and send the distal (left) pancreas for islet processing, while we continue to complete removal of the head of the pancreas.

In initial reports, TP was performed with preservation of the duodenum in the setting of a benign disease. However, this approach was associated with increased complications including stricture related to duodenal ischemia from disruption of the pancreaticoduodenal arcade. Partial duodenectomy is much more commonly performed in the setting of TP.

The spleen has important (though incompletely understood) immunological functions, and some centers routinely strive to preserve the spleen during TP-IAT. Splenic vessels are ligated near its hilum and blood supply is preserved via the short gastric vessels. Occasionally, anatomy is favorable to enable pancreatectomy without sacrificing the splenic artery and vein. However, with splenic preservation, there is a small risk of variceal transformation in the short gastric veins, which may lead to gastric bleeding, and incomplete perfusion may cause painful splenomegaly in the postoperative period. For this reason, we and other groups usually prefer to perform splenectomy during TP, especially in adult patients. Greater effort to preserve the spleen in children may be warranted.

TP is most often performed by an open laparotomy, although minimally invasive approach using a laparoscopic and/or robotic approach has recently been described.

After removal of the pancreas, gastrointestinal continuity is restored by choledochojejunostomy and either duodenogastrostomy or gastrojejunostomy, depending upon whether a pyloric preservation approach was used. The proximal jejunum is usually advanced in retrocolic fashion through the transverse mesocolon, and a biliary-enteric anastomosis is performed in an end-to-side configuration using a single layer of interrupted or

continuous fine absorbable suture, depending upon the diameter of the duct. An antecolic two-layered end-to-side duodenojejunostomy or Hofmeister-style gastrojejunostomy is preferred. The abdomen is then irrigated, the viscera are covered with a single moist laparotomy pad, and the abdominal wall temporarily covered with an occlusive iodine-impregnated transparent adhesive drape, while the islet preparation proceeds. Attention is given to maintenance of core body temperature and systemic fluid balance, while a low-dose insulin infusion is initiated to keep serum glucose in the 120-140 mg/dl range.

Pancreas processing

Immediately upon resection of the pancreas (or, sequentially, the pancreatic body/tail followed by the head/uncinate portion), it is promptly removed and placed into cold preservation solution. Blood is then flushed with preservation solution via splenic artery after opening a splenic vein. The pancreatic duct is then cannulated allowing digestion enzyme injection into the pancreas later on in the processing facility. The backbench preparation is complete when the duodenum and the spleen have been disconnected, and the pancreas is then packed in cold preservation solution and transported to the islet isolation laboratory. In the United States, islet isolation must be performed in a laboratory that meets all of the Food and Drug Administration (FDA) criteria (GMP- good manufacture practice) for processing human tissue.

The main goal of islet isolation process is to disrupt the exocrine pancreas and release relatively pure islet cells into a small tissue volume that can be safely infused. Briefly, the digestion solution containing collagenase is injected into the pancreatic duct using a perfusion machine to distend the organ. Next, the pancreas is divided into smaller pieces and gentle

mechanical dispersion is performed using the modified Ricordi method, freeing islets from the exocrine tissue. Upon completion of digestion process, the cell pellet is collected and islet cells are assessed for viability and counted under a microscope and islet mass is expressed as islet equivalents (IEQs) (Figure 3). The cell pellet is also tested for endotoxin content, and Gram stain is performed to determine sterility. In the setting of islet autotransplantation, it is not unusual for there to be microscopic and culture evidence of bacterial contamination, given that the patient has often undergone multiple medical, endoscopic, and/or surgical interventions such as gastric anti-secretory therapy, sphincterotomy, or anastomosis. It is our practice to avoid extended prophylactic antibiotic therapy despite positive Gram stain or culture, but we use the information for culture-directed antibiotic therapy if the patient shows early signs of postoperative infection.

Direct infusion of a large tissue volume into the portal vein may lead to varying degrees of intrahepatic microembolization, inflammation, and portal hypertension. To reduce the risk of these complications, some IAT centers further purify islet cells from acinar tissue when the pellet volume exceeds 0.25mL/kg body weight or 20 ml of tissue. It is important to remember that, inevitably, some islet mass will be lost during the purification process. Therefore, the benefit of decreasing the risk of large volume infusion must be weighed against the risk of lower islet mass leading to decreased graft function. On the other hand, in the setting of chronic pancreatitis, the pancreas is usually so fibrotic and atrophic that the tissue volume of the preparation is small enough that purification is usually unnecessary.

Islet infusion

During the islet isolation process, the patient remains in the operating room with the laparotomy incision temporarily covered after the reconstruction is completed. After islet processing is completed, the islet preparation is suspended in a balanced solution containing human albumin, placed into the infusion bag, and then transported from the islet lab back to the operating room. Surgical exposure of the portal vein is then obtained. Islets are then infused into the portal system under direct vision either via the stump of the splenic vein, by the umbilical vein, or via direct puncture of the portal vein (Figure 4A and 4B). Some groups prefer to close the patient's abdomen immediately after the reconstruction, leaving the islets to be cultured overnight and then infused post-operatively by a percutaneous approach under radiologic guidance.

Just prior to islet infusion, the portal pressure is measured at baseline, and it is then monitored intermittently throughout the infusion period. In general, portal pressure should not exceed 20-25mmHg. When a large tissue volume is infused, portal pressure will inevitably rise, potentially leading to reduction in blood flow and portal vein thrombosis.

Anticoagulation with heparin is typically used to prevent this complication. In our experience, when the islet volume less than 20 ml is infused into normal liver, portal pressure usually does not increase substantially. If portal pressure does rise above 25 mm Hg during islet infusion, it should be discontinued. The remaining islets are then either dispersed instead into the peritoneal cavity, or, preferably injected into the leaves of the mesentery, gastric submucosa, or intramuscular space, where at least some degree of islet engraftment might occur (this is unproven). Although islets transplanted into these alternative sites have been shown to survive in animal models, whether this approach is effective in the clinical setting is unproven.

Post-operative management

Most elements of postoperative management after TP-IAT are similar to any patient who undergoes major pancreatic resection. However, there are a number of important features of postoperative management that deserve specific comment. Because of the importance of tight postoperative glycemic control, patients are routinely admitted to the intensive care unit so that continuous insulin infusion may be safely administered. During the isolation process, islet vasculature is disrupted, and the islet cells are exposed to mechanical, osmotic, and hypoxic stress, leading to up-regulation of pro-apoptotic pathways. Also, in the immediate post-transplant period, the islet cells depend on diffusion of nutrients and oxygen until neovascularization occurs. Therefore, newly transplanted islet cells do not function fully for the first few weeks and require time for recovery and engraftment. Tight glycemic control is necessary to protect islets from toxic hyperglycemia during this period. Therefore, intensive insulin therapy with continuous insulin infusion is begun immediately with the goal that serum glucose is maintained at a target of 120 mg/dl. In the first few hours, a low continuous rate of 5% dextrose infusion may be necessary to avoid hypoglycemia. Typically, insulin infusion rates of between 0.5 and 2U per hour are used. After 48 hours, transition to subcutaneous injection is begun, beginning with a long-acting formulation, supplemented by sliding-scale and postprandial regular insulin. Patients are gradually weaned from insulin therapy over the course of 3-6 months if possible, as the autotransplanted islets achieve maximal function.

Extended prophylactic heparin or enoxaparin therapy is used for 30 days.

Postoperative pain management can be difficult in some patients and is best managed with a

team of expert acute pain specialists. Epidural, patient-controlled analgesia, local blocks, and ketamine infusion are particularly useful. Narcotic weaning must be carefully managed. After institution of oral diet, all patients require pancreatic enzyme replacement therapy, usually with coated enzyme preparations to achieve 72,000-96,000 IU lipase with meals, and lesser dose for snacks. Attention should be paid to the potential for fat-soluble vitamin deficiency, with routine multi-vitamin supplementation and periodic nutritional assessment.

Results of TP with IAT

The largest case series reporting TP-IAT outcomes have come from the University of Minnesota, the University of Cincinnati and the University of Leicester. The main endpoints of TP-IAT to consider include relief of pain, endocrine function and insulin independence, as well as overall improvement in quality of life.

Pain Relief and Quality of life (QOL)

The primary goal of TP-IAT is the relief of severe unrelenting pain associated with chronic pancreatitis. Many patients become dependent on narcotics preoperatively and the use of multiple high-dose formulations including continuous infusion is often encountered. It is not surprising, then, that the preoperative health-related QOL is significantly worse in chronic pancreatitis patients compared to the matched general population. Significant or complete pain relief after total pancreatectomy can usually be achieved in well-selected patients, with approximately two-thirds of patients achieving narcotic independence. Using a standard assessment tool (SF-36), the Cincinnati group has shown that QOL also improved

significantly following TP-IAT at mean follow-up of 19 months and remains improved over at least 5-10 years.

However, a significant minority of patients (approximately 10-20%) will continue to have persistent, minimally improved, or recurrent symptoms. The basis for failure is incompletely understood but includes continued substance dependence, central pain sensitization, and, on occasion, the possibility that the source of preoperative symptoms did not derive solely from the pancreas. Patients who continue to require narcotics postoperatively tend to have higher narcotic requirements pre-operatively as expressed in morphine equivalents (MEs). For patients with opioid hyperalgesia, narcotic independence may not be feasible. More studies are needed to identify patients at risk for opioid hyperalgesia and to develop effective methods for narcotic cessation.

Endocrine function

Overall, the reported postoperative insulin independence ranges from 10 to 40 percent, depending on the duration of follow up. For example, after 3-year follow up, a third of patients in the Minnesota series achieved insulin independence and another third of patients had partial graft function defined by positive blood C-peptide. Even though patients with partial graft function require insulin supplementation, overall glycemic control was improved, as HgA1c tended to be below 7 in vast majority of cases. In addition, the primary goal of IAT is to prevent brittle diabetes and its attendant hypo- hyperglycemic episodes, not necessarily to achieve insulin independence. Cincinnati, Leicester, and other centers have published similar results, with insulin independence in 22%-40% of patients. Although there is some attrition of islet function over time, long-term survival of islet autograft has been documented.

Although considerable variability exists among all the report series, islet yield tends to correlate with insulin independence. For example, in the Cincinnati series, the patients who achieved insulin independence received a mean of 6,635 IEQ/kg of body weight, whereas the patients who remained insulin dependent received a mean of 3,799 IEQ/kg of body weight. In turn, islet yield and quality depend on the quality of the pancreas. Advanced parenchymal damage caused by chronic inflammation and fibrosis lowers islet yield. In addition, prior pancreatic resection and pancreatic duct decompression (*e.g.*, following Puestow procedure) can decrease islet yield by up to 50%.

Therefore, overall endocrine function following TP-IAT depends on many factors including patient selection, duration of disease, any prior surgical procedure and quality islet processing, and factors related to successful engraftment. This suggests that deploying TP-IAT earlier on in the disease process may actually improve the endocrine functional outcome. However, the ability to achieve improved islet yield should not in itself be the major determinant of the timing or selection of TP-IAT.

Summary

In appropriately selected patients, TP-IAT achieves relief of pain and improves quality of life, while avoiding the risks of difficult-to-manage hyper- and hypo-glycemic episodes and, in a minority of patients, the possibility of insulin-independence. Candidates for TP-IAT should be counseled thoroughly regarding potential benefit (*i.e.* pain relief), and potential risk (*i.e.* lifelong exocrine insufficiency and likely type 3c diabetes). Setting of realistic expectations should be a priority for preoperative discussions. Although long-considered to

be an experimental treatment, the reported outcomes over the last 40 years have established TP-IAT as an effective treatment tool for chronic pancreatitis. TP-IAT is now covered by most third-party payers in the United States and, for some patients, is clearly now the standard of care. Many patients who suffer from chronic pancreatitis may benefit from earlier consultation for the possibility of TP-IAT.

Selected reading List

Bellin MD, Freeman ML, Gelrud A, et al.: Total pancreatectomy and islet autotransplantation in chronic pancreatitis: recommendations from PancreasFest. *Pancreatology*. 4(1):27-35 2014
PMID: 24555976

Bramis K, Gordon-Weeks AN, Friend PJ, et al.: Systematic review of total pancreatectomy and islet autotransplantation for chronic pancreatitis. *Br J Surg*. 99(6):761-6 2012 PMID: 22434330

Chinnakotla S, Beilman, GJ, Dunn, TB, et al.: Factors predicting outcomes after a total pancreatectomy and islet autotransplantation lessons learned from over 500 cases. *Ann Surg*. 262(4):610-22 2015 PMID: 26366540

Ong SL, Gravante G, Pollard CA, et al.: Total pancreatectomy with islet autotransplantation: an overview. *HPB*. 11(8):613-21 2009 PMID: 20495628

Wilson GC, Sutton JM, Abbott DE, et al.: Long-term outcomes after total pancreatectomy and

islet cell autotransplantation: is it a durable operation? *Ann Surg.* 260(4):659-65 2014 PMID: 25203883

Witkowski P, Savari O, Matthews JB.: Islet autotransplantation and total pancreatectomy. *Adv Surg.* 48:223-33 2014 PMID: 25293618

Tables

University of Minnesota Criteria for TP/IAT

Patient Must Fulfill Criteria Numbers 1–5:

1. Diagnosis of chronic pancreatitis, based on chronic abdominal pain of >6 mo duration and at least 1 of the following:
 - Pancreatic calcifications on computerized tomography scan.
 - At least 2 of the following: $\geq 4/9$ criteria on EUS, compatible ductal or parenchymal abnormalities on secretin MCRP; abnormal endoscopic pancreatic function tests (peak HCO₂ ≤ 80 mmol/L)
 - Histopathology confirmed diagnosis of chronic pancreatitis
 - Compatible clinical history and documented hereditary pancreatitis (PRSS1 gene mutation)
 - History of recurrent acute pancreatitis (more than 1 episode of characteristic pain associated with imaging diagnostic of acute pancreatitis and/or elevated serum amylase or lipase >3 times upper limit of normal)
2. At least 1 of the following:
 - Daily narcotic dependence
 - Pain resulting in impaired quality of life, which may include: inability to attend school, recurrent hospitalizations, or inability to participate in usual, age-appropriate activities
3. Complete evaluation with no reversible cause of pancreatitis present or untreated
4. Failure to respond to maximal medical and endoscopic therapy
5. Adequate islet cell function (nondiabetic or C-peptide positive)

EUS, endoscopic ultrasound; MCRP, magnetic resonance cholangiopancreatogram.

Table 1.

Bellin MD, Freeman ML, Schwarzenberg SJ, et al. Quality of life improves for pediatric patients after total pancreatectomy and islet autotransplant for chronic pancreatitis. *Clin Gastroenterol Hepatol.* 2011;9:793–799. (Table 1)

	Minnesota	Cincinnati	Leicester
Pancreatic Resection	Resected as a whole	Divided at the level of superior mesenteric artery with the distal pancreas sent for islet preparation during dissection of pancreatic head	Resected as a whole
Duodenum	Earlier series with complete preservation. More recently partial duodenectomy, preserving pylorus and D4	Partial duodenectomy with or without preserving the pylorus	Partial duodenectomy, preserving pylorus and D4
Spleen	Splenectomy in most cases	Routine splenectomy	Spleen preserving
Reconstruction	End-to-end duodeno-duodenostomy or end-to-side duodenojejunostomy. Choledochoduodenostomy	Side-to-side gastrojejunostomy or end-to-side duodenojejunostomy. End-to-side hepaticojejunostomy	End-to-end duodeno-duodenostomy or end-to-side duodenojejunostomy. Choledochoduodenostomy

Table 2

Ong SL, Gravante G, Pollard CA, et al. Total pancreatectomy with islet autotransplantation: an overview. HPB. 2009;11(8):613-21. (Table 2)

Figure Legends

Figure 1. Transplantation of islets in patients with chronic pancreatitis.

Witkowski P, Savari O, Matthews JB.: Islet autotransplantation and total pancreatectomy. Adv Surg. 48:223-33 2014 PMID: 25293618 (Figure 1)

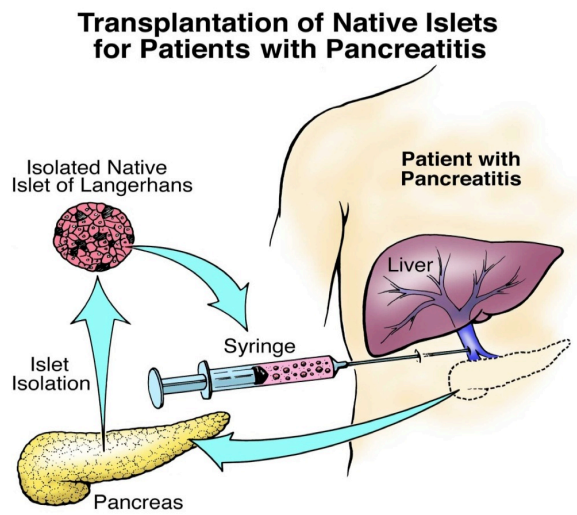


Figure 2. Total pancreatectomy specimen (a head and a body with tail) from a patient with chronic pancreatitis. Pancreatic duct is cannulated with angiocatheter allowing for subsequent perfusion with collagenase and organ digestion.

Witkowski P, Savari O, Matthews JB.: Islet autotransplantation and total pancreatectomy. *Adv Surg.* 48:223-33 2014 PMID: 25293618 (Figure 2A)

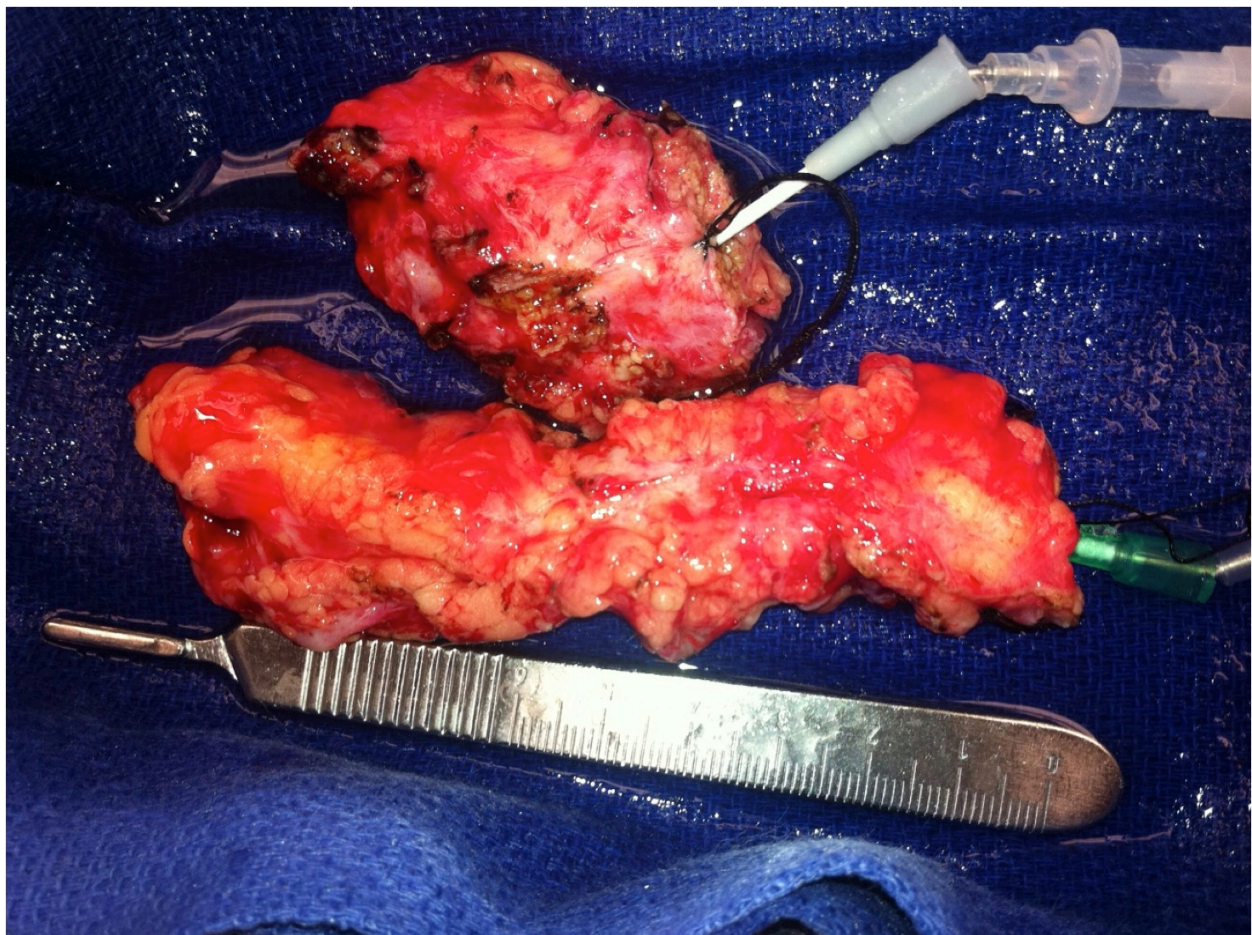


Figure 3. Pancreatic tissue following digestion seen under light microscopy. Islets stained with dithizone are in red and acinar tissue remains unstained in yellow-brown. (Magnification 30×).

Witkowski P, Savari O, Matthews JB.: Islet autotransplantation and total pancreatectomy. *Adv Surg.* 48:223-33 2014 PMID: 25293618 (Figure 2B)

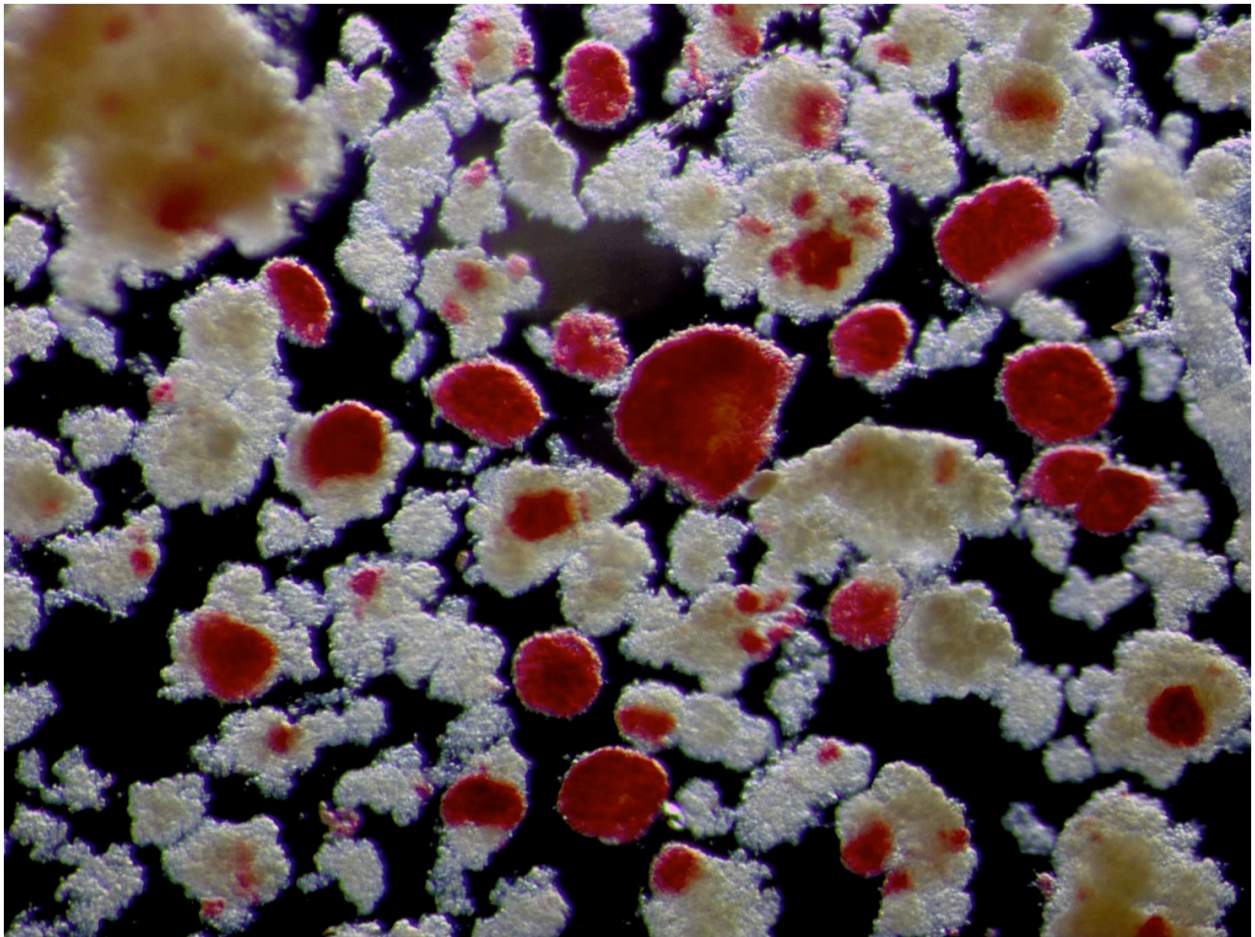


Figure 4A. Islet preparation in the infusion bag is seen in the foreground. Operative field is visible on the operating room monitor.

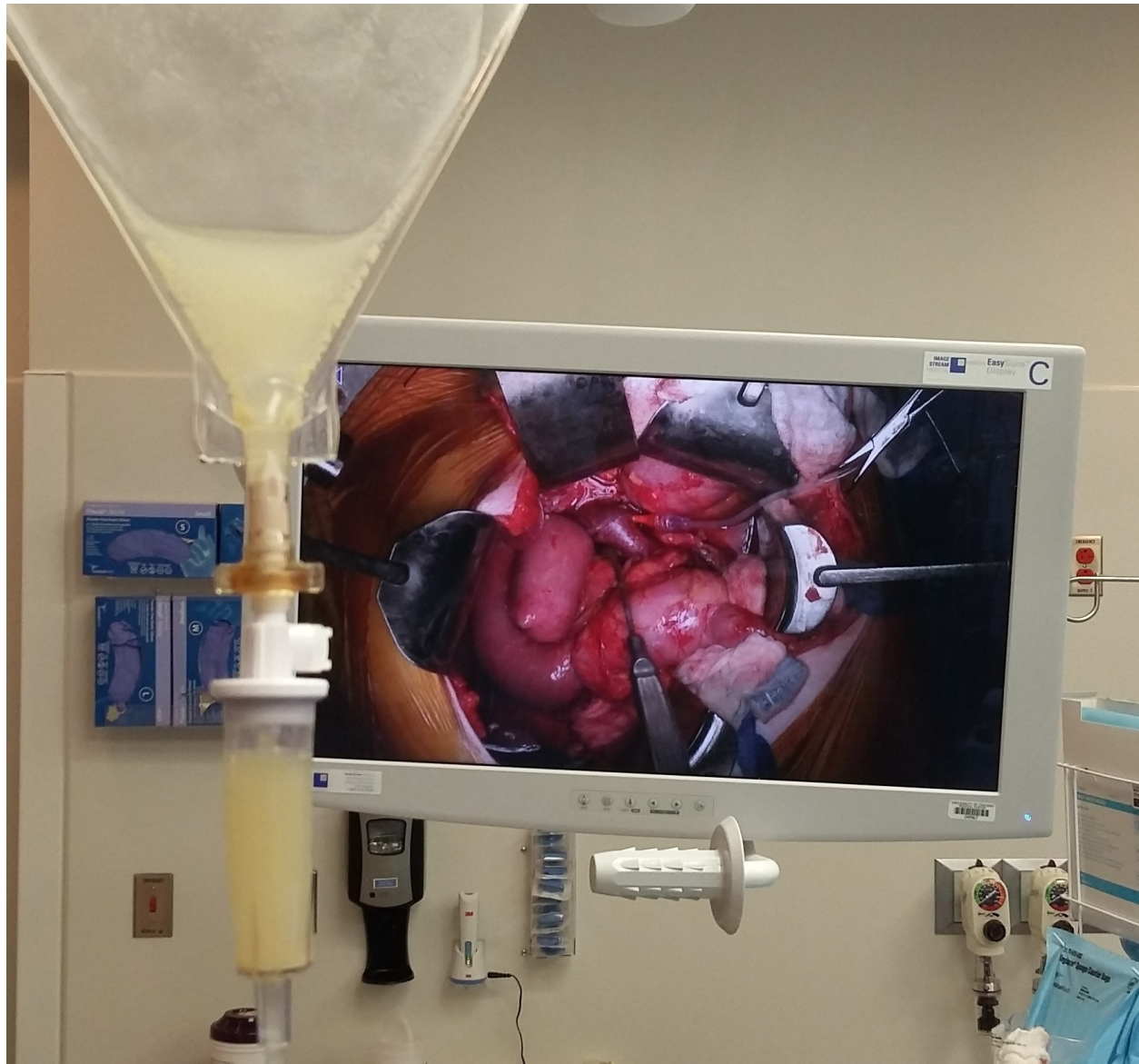


Figure 4B. Close up view of the operative field is shown. Portal vein was cannulated under direct vision with an angiocatheter for islet infusion.

