Total Pancreatectomy and Intrahepatic Islet Autotransplantation: Therapy for Chronic, Painful Pancreatitis

R. Paul Robertson*
Department of Endocrinology, Universities of Washington and Minnesota, USA

Perspective

From my perspective, it seems very odd that the surgical procedure of total pancreatectomy and autoislet transplantation (TPIAT) for patients suffering from chronic pancreatitis is almost unknown to the general medical community. TPIAT was first performed in 1980 and was immediately successful [1,7]. Now, over 35 years later, when I speak to medical audiences about this procedure, physicians and nurses almost to a person are amazed at what I tell them. Even gastroenterologists acknowledge they have very little knowledge about TPIAT although many will say they've heard of it. Still, the transplantation literature is replete with publications from all over the world that document the high success rate of TPIAT. It is true that internists and nurses and even general surgeons are not likely to put transplantation literature on the top of their reading lists, but even gastro-intestinal surgeons, who do read transplantation literature, in my experience, seem refractory to using TPIAT. They seem to favor repeated limited pancreatic resection of diseased areas. It’s a puzzle to me. More importantly, it’s a real problem for patients who elect to have the procedure. Many of them tell me it’s a tremendous problem for them when they return home from the transplant center where their TPIAT was performed because they cannot find a physician in the general community who is comfortable managing their post-operative course. It is common for autoislet recipients to be met with incredulity when they seek care at an emergency room or their local medical clinics for unrelated problems. They tell me the usual response they receive upon giving their surgical history to local caregivers is “That’s impossible. You cannot live without your pancreas. And you say somebody put your islets in your liver? That’s crazy!”

I write this Perspective because I am concerned about the lack of general information about the use of TPIAT for chronic, painful pancreatitis and on the chance that an endocrine--based surgical journal might be just the place to make this information more available to the general surgical/medical world. My experience over the past 30 years has been University of Minnesota-based and has involved post-transplantation pancreatic research with many TPIAT patients. I will use conclusions from peer-reviewed, published references from my and others’ groups [2-15] to try to make the case that TPAIT should be used much more often and much earlier for patients with chronic, painful pancreatitis than is currently the case. Let’s consider four questions [16-21].

Who are candidates for TPIAT? The criteria for TPIAT at the University of Minnesota are:

1) Chronic pancreatitis refractory to medical treatment and endoscopic interventions.
2) Narcotic dependence and/or significantly impaired quality of life.
3) Absence of medical/psychosocial contraindications to TPIAT.
4) The patient is either non-diabetic or has C-peptide positive diabetes.
5) The patient is willing to accept risk of diabetes to obtain pain relief.

Successful candidates spend a week at the transplant center learning about the procedure, its risks, and its possible outcomes, including death. During this visit extensive data are gathered by the transplant team with a major focus on the length and activity of pancreatitis; history of narcotic use to control pain; objective quality of life measures, including the ability to work, attend school and to provide childcare; use of tobacco or alcohol; and other concurrent illnesses. This information is considered by a team that includes transplantation surgeons, endocrinologists specializing in diabetes, gastroenterologists specializing in pancreas diseases and endoscopy, nurse and
What is surgically involved in the TPIAT procedure? Very generally and briefly stated, the patient is admitted to the center’s hospital, taken to the operating room for a total pancreatectomy with a proximal duodenum sparing approach that commonly involves a Roux-en-Y procedure, and is usually accompanied by resection of the spleen. The resected pancreas is taken to the center’s islet isolation laboratory where it is treated with a collagenase-type product and then cut into small pieces that are placed into a digestive apparatus for separation and isolation of pancreatic islets. The islets are purified by centrifugation and taken back to the patient who usually is still in the operating room where the islets are infused into the portal vein or one of its tributaries. The portal circulation carries the islets into the liver for distribution throughout the organ with careful monitoring of hepatic portal blood pressure. At this point the transplantation procedure is over, the abdomen is closed, and then the patient is taken to a post-operative care unit in the hospital.

What are the clinical outcomes in terms of patient survival, pain relief, islet survival, and prevention of diabetes? Patient survival in a University of Minnesota series of over 400 TPIAT autoislet recipients reviewed by Sutherland reports a patient survival rate of 1.2%. Pain relief was experienced in 80% to 86% of patients by 6 months to 3 years post-transplant. 50% of patients withdrew from narcotics in the first post-transplant year. Health-related quality of life (by objective measurements, such as the SF-36) improved. The key determinant in clinical outcomes is the amount of islets that are recovered from the resected pancreas. If a total of 350,000 islets or 5,000 islets/kg body weight (roughly one-third of the number of islets in a normal, healthy pancreas) are infused into the patient’s liver, the 2-year success rate for being free of insulin treatment and maintaining a HbA1c level <7.0% is approximately 70%. The duration of chronic pancreatitis is the key issue in recovering a sufficient number of islets because with time the acinar inflammation involves the islets and destroys them.

What is the functional status of intrahepatic islets post-transplant? Beta cell function, as measured by arginine-stimulation of insulin secretion, is quantitatively less than observed in normal control subjects [20] (Figure 1). However, when these data are corrected for the fact that the amount of islets transplanted in the liver are substantially less than the number of islets contained in the pancreases of normal controls, insulin secretion is of normal magnitude [20] (Figure 2). Alpha cell function in response to arginine is quantitatively equal to that observed in normal subjects [21]. However, the glucagon secretory response to hypoglycemia is virtually absent in TPIAT patients [21] (Figure 3). This is not the case, however, in TPIAT patients who received a portion of their islets in non-hepatic sites. These patients had normal glucagon responses to hypoglycemia. We have recommended the use of non-hepatic sites, such as the peritoneal cavity or omental sacs, because those recipients do have a normal glucagon response to hypoglycemia. This issue is of more than casual interest because maintaining the normal hypoglycemia-induced glucagon response is critical for TPIAT patients who need partial replacement therapy with exogenous insulin.

The main features of management of chronic pancreatitis that I hope comes through by writing this Perspective is that the TPIAT

**Figure 1:** Circulating insulin responses to a pulse of intravenous arginine before and during a concurrent infusion of glucose. The first response (AIRarg) was augmented by the intravenous glucose infusion so that the second response (AIRargMax) was greater and reflected insulin secretory reserve. The responses in the TPIAT patients, who had fewer islets, were significantly less than the controls [20].

**Figure 2:** The differences in responses shown in Figure 1 disappeared after correcting the AIRarg and AIRargMax values from the TPIAT group for the number of autoislets infused into their livers, which were approximately half of the number of islets assumed to be in the controls’ pancreas [20].

**Figure 3:** Circulating glucagon responses during a hypoglycemic, hyperinsulinemic clamp. TPIAT subjects who received autoislets in their liver failed to secrete glucagon as the circulating glucose levels were lowered from 70 to 50 mg/dl. However, intact glucagon responses in a subgroup a 5 TPIAT subjects who had received both intrahepatic and non-hepatic islets (mostly intraperitoneal) did have appropriate glucagon responses to insulin-induced hypoglycemia [21].
procedure needs to be more fully embraced by the surgical/medical community and it needs to be used much earlier in the disease than is currently the case. Many patients have had their disease for over a decade and have had many more endoscopic procedures for stenting than seems reasonable. Most patients only get temporary relief from pancreatic duct stenting. Other patients may undergo partial pancreas resection to remove the diseased portions of the gland. However, it has become obvious that surgery does not necessarily prevent recurrence of chronic pancreatitis and it also hastens the development of diabetes and limits the chances of recovering viable islets when a TPIAT is performed. For these reasons, the more reasonable approach seems to be an early, serious consideration of TPIAT if recurrent chronic, painful pancreatitis continues more than 2 years. It is not likely to improve by using less effective treatment for eight years more before turning to the more definitive treatment of TPIAT that has been shown to be successful in relieving pain, preventing diabetes, and improving quality of life.

Grant Support: NIH NIDDK RO-1 039994-27.

References