Published in final edited form as:

Curr Diab Rep. 2015 October ; 15(10): 67. doi:10.1007/s11892-015-0639-9.

Pediatric Autologous Islet Transplantation

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Abstract

A total pancreatectomy and islet autotransplant (TPIAT) offers substantial pain relief and improved quality of life for children who are severely affected by chronic or recurrent acute pancreatitis and for whom the usual medical and endoscopic therapies have failed. The pancreas is entirely resected, and the pancreatic islets are isolated from the pancreas and infused back into the patient's liver. Because this is an autologous transplant, no immunosuppression is required. Over several months, the islets engraft in the liver; the patient is then slowly weaned off insulin therapy. Slightly more than 40 % of patients become and remain insulin independent, yet even among patients who remain on insulin, most have some islet function, permitting easier diabetes control. The majority of patients experience pain relief, with significant improvements in health-related quality of life. A TPIAT should be considered for children who are significantly disabled by chronic pancreatitis.

Keywords

Pancreatitis; Islet autotransplant; Totalpancreatectomy; Chronicpancreatitis; TPIAT; Diabetes

Introduction

Rarely, children are afflicted with severe, debilitating chronic pancreatitis, usually due to underlying genetic predispositions to pancreatitis [1]. For those children, recurrent hospital visits, use of potent pain medications including narcotics, and loss of school time are common [1]. First-line therapies include medical management and endoscopic procedures,

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Compliance with Ethics Guidelines

Conflict of Interest Sarah J. Schwarzenberg, Marie Cook, David Sutherland, and Srinath Chinnakotla declare that they have no conflict of interest. Melena Bellin receives grant support from Dompe, Medtronic, and Merck.

Human and Animal Rights and Informed Consent Human subjects research has been performed by the authors under the approval of the institutional review board and with appropriate informed consent. This article does not contain any studies with animal subjects performed by any of the authors.

but they often fail to provide long-term pain relief [2]. A total pancreatectomy and islet autotransplant (TPIAT) might be the only therapeutic modality available to achieve sustained pain relief for children who are severely affected by chronic pancreatitis or by recurrent acute pancreatitis [3, 4•, 5, 6•].

While there are no registries or databases to track the number of TPIAT procedures performed, we estimate based on individual center reports that around 150 cases are performed in the USA each year, but the vast majority of these are performed in adult patients. At our institution, more than 100 such children have undergone a TPIAT (internal data) between 1989 (the first pediatric case, in a 12-year-old boy [3]) and 2014. Children undergoing TPIAT have ranged from 3 to 18 years of age.

Because it involves a major surgical procedure that confers a lifelong risk for diabetes, a TPIAT is appropriately reserved for children who are significantly affected by their disease—i.e., those who use narcotics, miss school, or are frequently hospitalized. The impact of this dual procedure is life altering, allowing return to school and normal function [4•, 5]. The goal of the *total pancreatectomy* is to relieve the intractable pain associated with pancreatitis; the *autologous islet transplant* is performed to prevent post-pancreatectomy diabetes mellitus or minimize its severity.

Screening Candidates

Careful consideration is given to screening patients to determine whether or not a TPIAT is the appropriate next step. Most children with chronic or acute recurrent pancreatitis are referred by their local pediatric gastroenterologist or interventional pancreatologist to a tertiary referral center experienced in specialized procedures like a TPIAT. At our institution, children are evaluated by a multidisciplinary team that includes a surgeon, gastroenterologist, endocrinologist, pain management specialist, child psychologist, and dietitian. Candidates are selected for surgery only after our multidisciplinary team discusses their eligibility, using previously published criteria [5]. Specifically and briefly, those criteria include the following: (1) characteristic abdominal pain and clear preceding history of recurrent acute pancreatitis or imaging features of chronic pancreatitis on magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasound (EUS), (2) failure of appropriate medical or endoscopic treatment, (3) lack of other medical or psychosocial contraindications, and (4) nondiabetic status or C-peptide-positive diabetes. The postoperative recovery is long, with a complex regimen of care, so adequate family support and treatment of mental health comorbidities are essential, in order to optimize the likelihood for a successful surgical outcome.

The most common risk factor for pancreatitis in children undergoing a TPIAT is the occurrence of predisposing genetic mutations [4•, 7•, 8] (Table 1). In fact, 54 % of children who have undergone a TPIAT have hereditary or genetic pancreatitis; that figure might even underestimate the proportion with genetic disease, since genetic testing was not available for the earliest patients [4•]. Mutations in the trypsinogen gene (PRSS1) are most common, predisposing to inappropriate activation of trypsin within the pancreas and thus precipitating progressive recurrent pancreatitis [9, 10]. Other predisposing mutations include loss of

trypsin inhibitor function (SPINK1 gene mutations) and cystic fibrosis transmembrane receptor (CFTR) gene mutations; with CFTR gene mutations, reduced bicarbonate secretion leads to intraductal obstruction, resulting in pancreatitis [11]. In the absence of an identified genetic risk factor, predisposing factors for pancreatitis in this population include pancreas divisum, idiopathic disease, and rarely other identifiable causes. Trauma is a common cause of acute pancreatitis in children, and at least once case of partial pancreatectomy with IAT has been performed following traumatic pancreatitis requiring surgical intervention [12].

Most children with chronic pancreatitis are nondiabetic, but they have a high lifelong risk of diabetes mellitus [13, 14]. The preoperative evaluation should include assessment for diabetes, to include, at a minimum, fasting glucose and hemoglobin A_{1c} levels. Oral or intravenous stimulatory tests, with fasting and stimulated C-peptide, provide more detailed information on islet function and might help estimate the likelihood of successful islet isolation [15, 16]. At our institution, we commonly perform mixed-meal meal tolerance tests. Intravenous stimuli can include either intravenous dextrose or arginine to elicit a first-phase insulin response that might correlate more directly with islet mass [16–18]. Preoperatively, immunizations against Meningococcus, Pneumococcus, and Hemophilus influenza are documented or completed because of anticipated asplenia.

Surgical Procedure

For children undergoing an islet autotransplant, the main variation in the surgical technique is preserving the blood supply to the pancreas until the dissection is completed for resection, in order to minimize warm ischemia time and maximize islet cell preservation. In addition, special attention must be paid to avoid any inadvertent injury or spasm of the small vessels to the pancreas, to preserve the pylorus, and to use a Roux-en-Y loop for duodenojejunostomy. Doing so minimizes postoperative gastrointestinal complications, such as bile reflux gastritis and ascending cholangitis.

For the gastrointestinal reconstruction, the proximal jejunum is mobilized and brought into the infrahepatic region on the right side. An end-to-side choledochojejunostomy is constructed (i.e., from the end of the bile duct to the side of the jejunum), using multiple interrupted absorbable sutures. Then, 20 cm downstream, the jejunum is divided, using a gastrointestinal anastomosis (GIA) stapler. A 40-cm Roux-en-Y limb is fashioned. An end-to-side duodenojejunostomy is constructed in two layers, using multiple absorbable interrupted sutures. A gastrojejunostomy tube is placed in the stomach, using the Stamm technique; the tip of the jejunal tube is placed in the distal jejunum.

At our institution, for the more than 100 children who have undergone a TPIAT, the entire procedure lasted 9.8 ± 1.1 h, including the islet preparation time of 4.8 ± 0.1 h.

Islet Isolation and Infusion

In the USA, islet isolation must be performed in a facility compliant with Food and Drug Administration (FDA) Good Manufacturing Practices. Most often, islet isolation is performed at the same institution as the surgery and islet infusion, but recently, several groups have performed TPIAT using a remote, off-site isolation facility [19]. In either case,

the pancreas is transported in preservation solution, either University of Wisconsin (UW) or something similar. The pancreas is distended with a collagenase-neutral protease enzyme blend infused via the pancreatic duct [20]. The pancreas is mechanically digested, using the semiautomated method of Ricordi [21].

COBE purification (COBE Laboratories, Inc., Lakewood, CO) can be performed to reduce final tissue volume, further separating islets from residual exocrine tissue by density centrifugation [22]. However, this process can be associated with islet loss, particularly in children, whose islets are often embedded with a rim of surrounding exocrine pancreas tissue. Our protocol has been to perform purification steps only when needed to reduce the tissue volume below 0.25 mL/kg, a threshold below which risk for portal hypertension and portal thrombosis is lower [23, 24].

Islets are stained with dithizone for counting. Islet mass is commonly expressed as total islet equivalents (IEQ) and/or IEQ per kilogram body weight of the recipient (IEQ/kg). IEQ represents the islet mass standardized to the size of a medium-sized islet (150 microns).

Islets are suspended in albumin-based media (Connaught Medical Research Laboratories-1066 medium; Mediatech, Inc., Manassas, VA) and returned to the operating room. They are infused under gravity into the portal vein, with careful monitoring of portal pressures. If portal pressures exceed 25 cm H₂O, or if tissue volume exceeds 0.25 mL/kg, then a final portion of the islets is often infused into a second site (classically, the peritoneal cavity) to minimize the risk for portal vein thrombosis. To date, with our protocol, we have not observed portal vein thrombosis related to islet infusion in any pediatric patient [24].

The intrahepatic site remains the preferred site for islet transplants, given the wealth of long-term data using it. But other sites have been used, for either a portion or all of the islet graft, including the peritoneal cavity, the stomach subserosa, and the intramuscular sites [25, 26, 27••]. The liver may have a particular disadvantage for alpha-cell function. We have observed that patients with intrahepatic grafts have normal basal glucagon levels, but their glucagon levels are not elevated, as would be expected with hypoglycemia. In contrast, when some islets are placed outside the liver, the normal counterregulatory response of glucagon to hypoglycemia is preserved [27••]. Other theoretical disadvantages to the liver include the potential exposure to the instant blood-mediated inflammatory response (IBMIR) which may result in inflammatory damage and thrombosis when islets are introduced directly into the portal blood stream [28]. However, to this date, the intraportal route remains the preferred site for clinical autoislet transplantation, given the experience with this site, the ease of access, the very well-established utility of this site for restoring beta cell function, and the theoretical advantage of immediate access to portal blood which allows at least limited diffusion of oxygen and nutrients before revascularization occurs [29, 30].

Early Postoperative Care

Children undergoing a TPIAT have been previously treated with narcotics, often at high doses for their age, so the close involvement of a pain specialist is crucial to establish adequate pain control after surgery. Transient delayed gastric emptying is common

postoperatively; appropriate attention should be given to meeting nutritional needs for surgical recovery. At our institution, we initiate continuous jejunal feeds, continued for 1 to 2 months after surgery. We use non-enteric-coated pancreatic enzymes in the jejunal feeds and enteric-coated pancreatic enzymes with meals, once the patient begins to eat orally. Fat-soluble vitamins are provided as a water-miscible product. Bacterial contamination of the pancreas or islet product is common; it is treated with antibiotics, but conveys no adverse long-term risk when treated appropriately [31, 32]. Children are managed by a multidisciplinary team on a ward with nurses experienced in the post-operative management of TPIAT.

During the process of islet isolation, the islets are necessarily devascularized from their rich arterial blood supply from the pancreatic artery. Therefore, the newly infused islets require at least several weeks, up to 3 months, to engraft and revascularize in the liver [33, 34]; during this time, beta-cell apoptosis is common and is exacerbated by hyperglycemia [35, 36]. Care must be taken to provide appropriate insulin therapy—by intravenous drip and then by subcutaneous injections—in order to maintain normal or near-normal blood glucose levels while the islets engraft [37•]. Patients should be followed closely by a multidisciplinary team, including the surgery, gastroenterology, endocrinology, and pain management services.

Remission of Diabetes

Eventually, more than 40 % of children will wean completely off insulin therapy after a TPIAT, usually in the first year after surgery, as compared with 20 % of adults (Fig. 1) [4••]. More extensive pancreatic damage, reflected in severe fibrosis on histopathology, is associated with lower islet yields and a lower likelihood subsequent insulin independence [38, 39]. Most patients who remain on insulin therapy have partial islet graft function, insufficient to be insulin-independent but benefiting overall glycemic control. The children who do become insulin-independent often remain so on a long-term basis; however, our follow-up time so far, for most of our pediatric TPIAT patients, is limited to 10 years [4••]. In any patient (adult or child), the longest documented duration of insulin independence (with normal hemoglobin A_{1c}) after a TPIAT is 16 years [40]. Because of the risk of islet attrition, lifelong monitoring of diabetes is mandatory, particularly during times of illness or stress. Medications that induce hyperglycemia, such as corticosteroids, are avoided whenever possible [41].

Insulin independence after a TPIAT is more common in children younger than 12 years [4••, 42]. We do not know whether this finding, in these smaller insulin-sensitive patients, reflects a higher potential for survival of islet mass, beta-cell regeneration, or a better environment for islet engraftment. Multiple reports, in both adults and children, have clearly documented that transplanting a higher islet mass increases the likelihood of insulin independence [29]. For children, each increase of 100,000 IEQ in the total islet mass increases the odds of insulin independence by about 2.6-fold [4••].

Nonetheless, for any given islet mass transplanted, diabetes outcomes vary. Even some patients with very few islets transplanted become insulin independent [29, 42, 43]. Islet

survival (engraftment) varies among islet recipients, so do insulin requirements and insulin sensitivity. Prior surgical drainage (the Puestow procedure or a lateral pancreaticojejunostomy) reduces the islet mass isolated by about half, highly increasing the risk of diabetes mellitus after a TPIAT [4•, 29]. At our institution, we generally recommend avoiding such procedures in patients with genetic disease when an eventual TPIAT is probable.

Importantly, after a TPIAT, patients maintain, on average, near-normal blood glucose levels. The mean hemoglobin A_{1c} in this population is under 6 % at 3 and 5 years after surgery, regardless of insulin requirements [4•]—a level of control that is not feasible in patients with routine type 1 diabetes (i.e., those who have complete insulin deficiency states) even with excellent adherence [44].

Quality of Life and Pain Resolution

The primary objective of a TPIAT is to allow children to return to normal life free of severe, incapacitating pain. In this respect, TPIAT is successful for the vast majority of patients. At our institution, about 80 to 90 % of them consistently experience pain remission or significant pain reduction, with freedom from narcotics, 1 year postoperatively [4•]. Hospital admissions, emergency room visits, and school absence is reduced dramatically. Health-related quality of life, as assessed by the Short Form-36 (SF-36) survey, improves in all subscale measures of physical and mental/emotional health, with the most dramatic improvements seen in the physical role and bodily pain scores [4•, 5].

Long-Term Considerations

After a TPIAT, as children grow, close attention should be given to adjusting their pancreatic enzyme replacement therapy. The general target is a dose of 1000 to 2000 lipase units/ kg/ meal (range, a minimum of 500 to a maximum of 2500 lipase units/kg/meal). Excessive doses should be avoided to prevent fibrosing colonopathy. Enzyme dose adherence, symptoms of diarrhea or steatorrhea, and weight gain should be reviewed at each follow-up visit. Linear growth needs to be monitored as well. Although anecdotally we have observed normal growth and development in children after TPIAT, linear growth and weight gain after TPIAT still need to be formally studied, particularly in young children.

Constipation is a relatively common problem that can cause episodes of abdominal pain [45]. It should be noted that pancreatic enzyme therapy does not cause constipation. Levels of fat-soluble vitamins (A, D, E), vitamin B₁₂, and iron are assessed after surgery, at 3 months, at 6 months, at 1 year, and then, if levels are stable, yearly [46]. Multivitamins containing water-soluble forms of vitamins A, D, E, and K are preferred over standard multivitamins.

Children who undergo a splenectomy (currently, at our institution, all children undergoing a TPIAT) need to receive appropriate care and guidance for asplenia. Immunizations are administered according to the US Centers for Disease Prevention and Control (CDC) and the American Academy of Pediatrics Red Book guidelines [47]. Current requirements before a splenectomy include immunization against pneumococcus, meningococcus, and

Haemophilus influenzae type b and then yearly administration of the seasonal influenza vaccine. In addition, in accordance with the most recent Red Book guidelines, children should receive antibiotic prophylaxis with amoxicillin for 1 year after a splenectomy, until they are at least 5 years old. Patients and parents should be counseled to receive urgent medical attention for fevers and to seek out physician counseling before traveling to areas with endemic malaria.

Because of the lifelong risk of developing diabetes, even insulin-independent patients should continue to monitor blood sugar levels. For those on insulin therapy, standard diabetes management guidelines should be followed. For those off insulin therapy, we recommend both a fasting glucose test and a 2-h postprandial test daily or, at a minimum, several days per week; frequency of monitoring should be increased to 3 to 4 times per day with illness, surgery, or other severe physical stress. Transplanted islets appear to incur loss under conditions of hyperglycemia, presumably because of glucotoxicity and stress on the marginal islet mass, so we postulate better long-term preservation if insulin therapy is quickly restarted at the onset of hyperglycemia. Our institutional guidelines are to administer insulin therapy if the hemoglobin A_{1c} rises above 6.5 %, if fasting glucose levels are recurrently above 125 mg/dL, or if the 2-h postprandial glucose levels are above 150 to 180 mg/dL. At least once a year, we measure islet function as well as hemoglobin A_{1c}; however, doing so more often (every 3 to 6 months) is ideal, even in insulin-independent patients, as an assessment for hyperglycemia.

Conclusions

In conclusion, a TPIAT might be the only option for achieving sustained pain relief and returning to a normal quality of life for children who are severely affected by chronic or recurrent acute pancreatitis and for whom medical and endoscopic therapies have failed. At our institution, most of the children that we have seen for this procedure have genetic mutations in trypsin pathways or in bicarbonate secretion (CFTR) that account for their severe disease. Because of the complexity of this procedure, which requires multiple components of medical care, a multidisciplinary team is needed, including surgery, gastroenterology, pain management, psychology, and endocrinology. Preoperatively, patients and families must be thoroughly evaluated and educated; postoperatively, appropriate care and long-term follow-up are essential. About 85 % of children experience pain relief, no longer need narcotics, and enjoy a restored quality of life. Slightly more than 40 % become and remain insulin-independent, and even among patients who remain on insulin, most have some islet function, permitting easier diabetes control. Even in insulin-independent patients, lifelong monitoring is needed to assess for any changes in terms of diabetes, exocrine insufficiency, asplenia, and nutrition (including micronutrient levels).

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Fig. 1. Insulin-independence rates after a TPIAT, in pediatric ($n=91$) vs. adult ($n=490$) patients

Table 1

Common risk factors precipitating recurrent acute and chronic pancreatitis in children who undergo TPIAT

Genetic mutations
Trypsinogen gene mutations
PRSS1
Trypsinogen inhibitor mutations
SPINK1
CTRC
Mutations leading to defects in ductal secretion of bicarbonate
CFTR
Anatomic abnormalities
Pancreas divisum
Annular pancreas
Idiopathic disease
Other causes (rare)
Medication related
Trauma
Sphincter of Oddi dysfunction

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