

REVIEW ARTICLE

Is Total Pancreatectomy with Islet Autotransplantation A Reasonable Choice for Pediatric Pancreatitis?

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ABSTRACT

Chronic pancreatitis is an emerging and poorly understood disease in childhood. Total pancreatectomy with islet cell autotransplantation is being proposed as a treatment for chronic pancreatitis and recent studies report a more favorable outcome in children compared to adults. Herein, we review the therapeutic alternatives for pediatric chronic pancreatitis, focusing primarily on TP/IAT.

Introduction

Chronic pancreatitis (CP) is a progressive inflammatory process of the pancreas that results in irreversible structural changes, loss of parenchyma and fibrosis, leading to exocrine pancreatic insufficiency (EPI) and diabetes [1]. Children with acute recurrent or chronic pancreatitis often have mutations in the cationic trypsinogen (*PRSS1*), cystic fibrosis transmembrane generator (*CFTR*), serine protease inhibitor Kazal type I (*SPINK1*) and carboxypeptidase 1 (*CPA1*) genes [2-8]. A strong association between *CPA1* mutations and childhood-onset CP [8] suggests that genetic risk factors may determine early onset of CP. The genetic variants in the claudin 2 (*CLDN2*) [9], and chymotrypsin C (*CTRC*) genes [10], carboxylesterlipase (*CEL*) and *CEL-*

HYB allele (originating from a crossover between *CEL* and its neighboring pseudogene, *CELP*) [11, 12] increase the risk for CP in adults with idiopathic CP or already have alcohol and smoking as risk factors. Most high-penetrance *PRSS1* variants increase intrapancreatic trypsin activity by stimulating trypsinogen autoactivation and/or by inhibiting *CTRC*-dependent trypsinogen degradation [13]. Alternatively, some gene mutations (*PRSS1* variants, *CEL-HYB*, pancreatic triglyceride lipase (*PNLIP*), *CPA1*) can cause protein misfolding, which results in intracellular retention/degradation and consequent endoplasmic reticulum stress [8, 11, 13, 14].

The persistent abdominal pain, exocrine pancreatic insufficiency (EPI), diabetes, repeated hospitalizations and procedures, result in overall impaired quality of life (QOL) in children with CP [15-17]. The recurrent exacerbations and unrelenting pain may lead to depression and narcotic analgesic dependence. Patients with hereditary pancreatitis have a high life time risk of EPI, diabetes and pancreatic adenocarcinoma (up to 40%) [18-20]. The diabetes occurs in ~5% of patients with hereditary pancreatitis by 10 years after the onset of symptoms, and 18% by 20 years [18]. This form of diabetes is called type 3c or pancreatogenic diabetes and is the result of partial or complete loss of insulin secretion. The treatment of pediatric CP should be directed at the complications, including chronic pain, EPI and diabetes. This review focuses on total pancreatectomy with islet cell autotransplantation (TP/IAT) as a therapeutic alternative for pediatric CP.

TOTAL PANCREATECTOMY WITH ISLET AUTOTRANSPLANTATION (TP/IAT)

Although TP/IAT is being performed in increasing numbers in children, the literature is limited to publications from a few single centers. In general, the studies are retrospective, study populations are small, and the duration of follow-up is relatively short. The self-reported or guardian-reported

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Abbreviations *CFTR* cystic fibrosis transmembrane conductance regulator; CP chronic pancreatitis; *CTRC* chymotrypsin C; *CPA1* carboxypeptidase-1; *CLDN2* claudin 2; *CEL* carboxylesterlipase; *PNLIP* pancreatic triglyceride lipase; *ERCP* endoscopic retrograde pancreatography; INSPPIRE International Study Group of Pediatric Pancreatitis: In search for a cure; *PRSS1* protease, serine 1; *SPINK1* serine protease inhibitor Kazal-type 1; TP/IAT total pancreatectomy with islet autotransplantation; IEQ islet equivalent; PERT Pancreatic enzyme replacement therapy; QOL quality of life; EPI exocrine pancreatic insufficiency

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measures (telephone surveys, mailed HbA_{1c} kits, self-recorded glucose levels) may introduce bias.

Total pancreatectomy (TP) is an irreversible operation and often reserved for diffuse pancreatic disease. It involves complete resection of the pancreas on the basis that removing the diseased organ would eliminate the pain. TP removes any cancer risk that those patients may harbor [18-20], but leaves patients deprived of the exocrine and endocrine functions of the pancreas. Whereas it may be relatively simple to substitute the exocrine function of the pancreas with pancreatic enzyme replacement therapy (PERT), replacing the endocrine function is more problematic. Some patients who undergo TP may develop brittle diabetes associated with hypoglycemia and hyperglycemia [21-34], which is particularly difficult to control.

The islet autotransplantation is designed to preserve the beta cell mass in patients undergoing TP. Islet autotransplantation after pancreatectomy was first performed for CP in 1977 [35] with the first pediatric application in 1989 [36]. Unlike the islet cell allotransplants, there is no need for immunosuppression post-operatively since the transplantation is autologous.

Technical Considerations

The largest series have been reported from the University of Minnesota, University of Cincinnati, Medical University of South Carolina and Leicester General Hospital [21, 23-28, 30-34, 36-44]. The procedure is most often performed by open laparotomy, but there have been few studies using robotic assistance [40]. The first part of the procedure consists of total pancreatic resection, removing second portion of the duodenum, distal common bile duct, and often the spleen, appendix and gallbladder [24, 32, 34]. The bowel continuity is restored with duodenoduodenostomy or duodenojejunostomy and bile continuity with choledochoduodenostomy or chledochojejunostomy. The removed pancreatic tissue is sent for islet cell harvest.

The success of islet isolation depends on an efficient delivery of collagenase enzymes for pancreatic digestion and removal of acinar and ductal tissue. It is challenging to obtain high quality islet yields from fibrotic, calcified tissues of CP. Optimizing perfusion of the collagenases by clamping pancreatic duct leaks may increase the number of isolated islets [45]. Some suggest adjusting the dose of collagenase enzymes for patient's age and amount of pancreatic fibrosis [46]. A new enzyme mixture consisting of collagenase and neutral proteases has also been proposed to optimize the islet yield [47, 48]. The pancreatic homogenates are then subjected to density gradient purification to purify islets and remove the unwanted exocrine tissue and digestive enzymes [49].

One purified, islets are counted and assessed for viability. The islet yield is quantified in terms of islet equivalents (IEQ), which is the islet mass standardized to an islet size of 150 μ m. Obtaining high quantity and excellent quality islets from CP remains a challenge and further refinement of the procedures is required.

After a lengthy isolation and possibly purification process, islets are infused into the hepatic circulation via the portal vein. The islet autotransplantation is currently performed at over 15 academic institutions in the US [50]. The procedure requires unique technical expertise and adherence to strict Food and Drug Administration (FDA) standards for Good Manufacturing Practice involving processed tissue samples.

The animal models have suggested that early hyperglycemia results in impaired revascularization, islet apoptosis, and a substantial reduction in islet mass following transplantation [51-53]. Hence, the patients receive insulin post-operatively, often for three months, to maintain euglycemia and allow the islets the opportunity to engraft and vascularize without functional stress. Insulin is later weaned while keeping satisfactory glucose and HbA_{1c} levels (fasting blood sugar <126 mg/dL, postprandial blood sugar <180 mg/dL, and HbA_{1c} \leq 6.5%). Other considerations include administering pre-splenectomy vaccinations, initiating PERT, fat-soluble vitamins, and adequate pain control before the procedure.

The portal venous pressure may increase transiently with islet infusion [39, 41]. Although 3-4 % risk of partial portal venous thrombosis can be observed [54], no serious sequelae have been reported in children. If the portal venous pressure becomes persistently high during IAT, the remaining islet cells are often infused into the peritoneal cavity or injected into the mesentery, omentum, bowel subserosa, gastric submucosa or intramuscular space [21, 23]. Although islets transplanted at these alternative sites have been shown to survive in animal models [55], there are no clinical studies comparing islet function and survival between liver vs. other locations. Bellin et al. have shown more physiological glucagon responses to hypoglycemia in patients who received both hepatic and non-hepatic islet transplantation compared to hepatic infusion alone [66]. It is encouraging that the intramuscular islet autotransplantation in a 7-year-old child with hereditary pancreatitis resulted in low insulin requirements and C-peptide positivity for more than 2 years [56]. More studies are needed to establish the best location for islet engraftment and functioning.

Almost half of the islets may be lost during the infusion due to a non-specific inflammatory and thrombotic reaction called instant blood-mediated inflammatory reaction (IBMIR) [57]. IBMIR is characterized by platelet consumption and activation of the coagulation and complement systems. Techniques that minimize IBMIR (i.e. culturing islets with low molecular weight dextran sulfate) will diminish the early loss of islets [57]. More studies are needed to define the factors that affect islet cell survival after transplantation.

Indications

Currently, there are no consensus guidelines for TPIAT eligibility, but parameters that have been developed by individual centers (summarized in Table 1). In general, the

children with intractable abdominal pain due to CP who failed other therapies are candidates for this operation. There may be a lower threshold to select patients with *PRSS1* mutations because of the risk for pancreatic cancer in the future. The decision for TPIAT requires a multidisciplinary team including pediatric gastroenterologists, pediatric surgeons, pediatric endocrinologists, psychologists, and anesthesiologists. The child's physical and emotional status in coping with and managing diabetes must be assessed.

In a rare child who presents with CP and diabetes, TP/IAT may still be considered if the diabetes is mild (C-peptide positive) and there is no evidence of autoimmune diabetes (negative islet autoantibodies) to avoid the development of brittle diabetes in the future [23, 30, 45]. C-peptide values from mixed meal tolerance testing may be useful in predicting the islet cell yield in these children [23, 30]. Intravenous arginine stimulation testing may assess the number of engrafted islets post-transplant [58]. Pros and cons of TP/IAT in children with CP are summarized in Table 2.

Outcome

The most important measure of success after TP/IAT is pain relief while preserving the pancreatic endocrine function. Other endpoints include narcotic independence, QOL, post-operative complications and survival. Below is the summary of outcomes reported in pediatric patients after TP/IAT.

Pain Control

All patients receive IV opioids immediately after surgery that is later changed to oral analgesics. According to studies from the University of Minnesota, the pain improves gradually in children who undergo TP/IAT. Most of this improvement takes place within the first year, with 50-80% of patients becoming narcotic independent on follow-up [21, 26, 29, 32, 33, 43]. The pain improvement is largely sustained at 10-year follow-up, whereby 10-20% of patients continue to take narcotics [32, 33]. In general, the preadolescent children have better responses compared to adolescents (89% achieve narcotic independence vs. 33%) [21, 25]. Chronic narcotic use can result in opioid-induced hyperalgesia and make the postoperative weaning of pain medications challenging [59].

Pancreatic Endocrine Function

In general, higher islet yields are associated with better graft function and a higher likelihood of insulin independence [37, 41]. Patients are more likely to achieve insulin independence if islet yield is over 5,000 IEQ/kg body weight or a total of 100,000 IEQ [29, 32, 33, 45].

The islet yield is strongly influenced by the histopathological changes in the pancreas [25, 33, 41, 60]. IEQ per body weight is significantly lower in the presence of advanced pancreatic fibrosis, acinar atrophy and hereditary/genetic pancreatitis. There is no correlation between the islet yield and the type, degree, location of inflammation, distribution or location of fibrosis or acinar

atrophy [25]. Islet yield may be predicted by fasting blood glucose, HbA1c and C-peptide levels prior to surgery [23].

A history of previous pancreatic surgery is inversely correlated with insulin independence, with distal pancreatectomies and drainage procedures (i.e. Puestow procedure) being strongly associated with worse outcomes at the University of Minnesota [24, 26, 33, 52]. This is explained by the fact that partial pancreatectomies remove as much as half to two thirds of the pancreas and thus the islets, whereas drainage procedures dissect the pancreatic duct which could compromise the intraductal perfusion of enzymes during islet isolation [21, 24]. Severe fibrosis and acinar atrophy were found in the pancreas of patients who underwent a prior drainage operation, but it is not known whether this is directly related to the intervention itself or indirectly through delaying TP/IAT while CP progressed [25]. There was no difference in islet yield of children with previous pancreatic surgeries vs. those who did not at the University of Cincinnati [43], but the numbers were small. Autotransplanted islets do not resume full function immediately after surgery. They depend on the diffusion of oxygen and nutrients until neovascularization occurs in 2-4 weeks [61, 62].

The blood glucose is closely monitored during and after surgery and strictly controlled with insulin to avoid possible detrimental effect of hyperglycemia on islet engraftment. In general, the islet cell function after TP/IAT is assessed indirectly by the need for insulin. However,

Table 1. Patient selection for TP/IAT

Common Indications
<ul style="list-style-type: none"> • CP with refractory abdominal pain and significant derangements in QOL despite medical or surgical interventions • Hereditary CP
Relative contraindications
<ul style="list-style-type: none"> • Preexisting type 1 or type 3 diabetes (C-peptide negative) • Preexisting liver disease • Portal hypertension • Portal vein thrombosis • Psychosocial issues/narcotic dependence • Systemic diseases involving circulatory and respiratory systems

Table 2. Pros and Cons of TP/IAT in pediatric CP

Pros
<ul style="list-style-type: none"> • Potential resolution of chronic refractory abdominal pain • Improved QOL • Removal of pancreatic cancer risk
Cons
<ul style="list-style-type: none"> • High cost • Prolonged hospital stay • Irreversible operation • Life-long dependence on exogenous pancreatic enzymes • Diabetes and potential life-long dependence to exogenous insulin • Absence of counter-regulatory hormones • Gastrointestinal side effects (dysmotility, malabsorption, maldigestion, diarrhea, constipation, malnutrition, etc)

insulin replacement does not substitute for all hormones of the pancreatic islets, including glucagon, somatostatin and pancreatic polypeptide.

In general, children undergoing TPIAT achieve higher rates of insulin independence (~50%) compared to adults (~30%) [21, 32, 43]. It is not known whether the superior response in pediatric patients is due to the extent of pancreatic disease or regenerative capacity of the islets. This could be the result of fewer pancreatic procedures performed on younger patients or shorter course of disease. Younger children (<12 years) are more likely to achieve insulin independence compared to older children [33]. However, it is unknown why the adolescents with shorter disease duration experience less favorable results compared to preadolescents. Poor engraftment, increased loss of islets, decreased islet function may be some of the factors leading to the unfavorable outcome in adolescents [21]. The prepubertal milieu may also be more protective of transplanted islets than that of puberty when insulin resistance is more prominent [25]. Based on the unfavorable results in adolescents compared to prepubertal children, early TP/IAT has been increasingly recommended.

The islet function persists in adults who undergo TPIAT, but the percentage of patients that remain insulin-independent declines over time [29, 38, 42, 60]. The decline is faster in patients with hereditary/genetic pancreatitis [33]. Similar to the narcotic independence, insulin independence is also generally sustained over the 10-year follow-up in the majority of children (~40%) [32]. It appears that transplanted islets are able to uphold their function despite patients' growth and development. It is unclear how islet cells compensate for the child's growth, and whether this is due to islet cell replication or neogenesis. Some reports have even raised the question of islet quality versus quantity [21]. The viability or function of the islets may deteriorate over time due to formation of beta cell autoantibodies [63] or amyloid deposition in islets [64]. To date, amyloid deposition has only been reported in islet allografts.

Quality of Life (QOL)

Chronic, relenting pain is common in children with CP. In a multicenter study led by INSPPIRE, ~80% of children with CP reported abdominal pain and the pain was constant requiring narcotic use in ~1/3rd [17]. Chronic pain is linked to anxiety, depression, low self-esteem, and overall decreased QOL. Children with CP and chronic pain experience frequent school absences, decreased social functioning and high level of fatigue [43, 65]. Chronic pain is the leading indication for medical, endoscopic and surgical interventions including TP/IAT.

Both children and adults demonstrate significant improvement in physical and mental health after TP/IAT [26, 33, 43, 66]. The QOL is reported as good to excellent in ~75% of children following TP/IAT, with a slight drop in QOL physical and mental measures ~ 6 months post-operatively that coincides with weaning from narcotics at

that time [21]. Two years after surgery, less than 10% of parents report lost school days compared to 87% before surgery. Limited activity days also significantly diminishes by 2 years after surgery [32]. The improvement in QOL is not as remarkable in adults [26].

Gastrointestinal Side Effects

The gastrointestinal symptoms are common complaints for patients with CP both before and after TP/IAT [31, 50]. Diarrhea is the most common complaint with a peak incidence at 6 months after surgery. Steatorrhea is also more prevalent at 6 months and 1 year post-surgically. Constipation is not commonly seen, possibly as a result of discontinuing narcotic therapy. Gastroparesis is common after TP/IAT as the enteric and biliary reconstruction may significantly alter gut motility [67]. The loss of exocrine pancreatic function after TP/IAT inevitably causes maldigestion and malabsorption of nutrients, which in turn impacts the glycemic control [68]. Children also experience weight loss post-operatively, therefore adequate PERT and fat-soluble vitamin replacement is vital in the care of these patients. PERT improves steatorrhea to some degree, but does not seem to have an impact on other GI symptoms. The challenges with PERT include cost, optimal dosing and compliance.

Pancreatic Cancer

TP removes the pancreas, therefore the risk for pancreatic adenocarcinoma associated with CP [18-20]. Very small amounts of acinar and ductal cells may be co-infused into the liver with the islet cell product [69]. However, there are no reports of pancreatic cancer after TP/IAT.

Morbidity and Mortality

Intraoperative complications may include: hypotension (15% patients requiring vasopressors), blood loss (350-1200 ml), hypothermia (39%) [39]. The post-operative care of the TP/IAT patient requires a dedicated team and close follow-up. In general, children are hospitalized an average of 16-24 days after surgery [21, 25, 43]. The immediate post-operative mortality is low (<2%) and in one case due to enteric perforation from a feeding tube, peritonitis and sepsis [29, 32]. In the largest series to date, the complications occurred in 20 children who underwent TP/IAT (20%), with urinary tract infections (17%), catheter related bacteremias (12.5%), and pneumonia (12.5%) being the most common. Overall, younger children (<12 years) tended to have lower complication rates compared to older children. Prior pancreatic surgery did not seem to affect post-operative complication rates [32]. Other post-operative complications are: intraabdominal hematomas/abscesses, splenic tear/bleeding, bile leak, pancreaticocutaneous fistula, gastrointestinal bleeding, median nerve injury, aspiration pneumonia (each <5%) [39].

The long-term survival after surgery is ~90% at five years, 81% at 10 years, and 62% at 20 years in both adults and children [29, 33]. The long-term mortality in most instances is unrelated to the surgery [60].

CONCLUSION

As mentioned earlier, the literature on TP/IAT in children is limited to few single center experiences. The operation is likely to be successful in a group of children with CP, but the long-term consequences of this operation are largely unknown. Therefore, the selection process should be handled with utmost care. Despite the increased use of TP/IAT for pediatric CP, especially within the last decade, many questions remain unanswered. The patient selection and timing of the procedure are the main quandaries. The limitation in the accurate diagnosis of CP is another important confounding factor.

The natural history of CP and the factors that predispose to rapid progression of disease (severe pancreatic fibrosis, EPI and diabetes) are not well-known in the pediatric age group. A better understanding of the natural history of CP in children may lead to the development of therapies that interrupt disease progression. It may also help identify the best timing to intervene.

The research priorities should focus on devising guidelines for diagnosing early CP, determining patients who would benefit from TP/IAT and identifying best timing for this operation if necessary [50]. Predicting the islet yields is a key factor in decision-making and pancreatic histological changes seem to correlate with the islet yield and insulin independence. Thus, the development of non-invasive or minimally invasive methods to assess pancreatic fibrosis is crucial to achieve this goal. Optimizing methods for islet isolation and improving islet engraftment, viability and longevity are other targets for future research. Improving QOL and returning to daily activities should be the benchmark of success following treatment.

Conflicting Interest

The authors had no conflicts of interest

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