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Total Pancreatectomy and Islet Auto-Transplantation in Children with Chronic Pancreatitis

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Introduction

Chronic pancreatitis (CP) is an uncommon diagnosis in children, with an estimated incidence of fewer than 0.5 cases per 100,000 in patients younger than 25 years [1]. Chronic pancreatitis in children most commonly results from genetic mutations, including mutations in the PRSS1, SPINK1, and CFTR genes [2,3]. A recent multinational cross-sectional study of children with chronic pancreatitis demonstrated genetic etiology in upwards of 67% of cases while obstructive etiology including biliary calculi and congenital anatomic abnormalities made up 33% [3]. Some of these patients had both genetic and obstructive etiologies and 11% of patients at no known risk factors at all (idiopathic). Congenital anatomic abnormalities associated with pancreatitis include pancreas divisum, annular pancreas, intestinal duplication cysts, anomalous pancreaticobiliary junction, and choledochal cyst [4-8].

The initial treatment of childhood CP includes narcotic analgesics, pancreatic enzyme supplementation to minimize pancreatic stimulation, nerve block procedures, and endoscopic decompression of obstructive disease by stone extraction, sphincterotomy, stricture dilation, and stent placement [9,10]. Children that fail medical or endoscopic interventions are surgical candidates. The various surgical interventions include partial resection (Whipple's procedure, distal pancreatectomy), drainage procedures such as lateral pancreaticojejunostomy (Puestow), or variants (Frey, Beger, or Duval procedures) [11]. Patients can obtain pain relief from these procedures, but due to the diffuse nature of CP, pain eventually recurs in up to 50% of patients; [12-17] Also, despite the aforementioned interventions, exocrine and endocrine insufficiency can still develop over time [18].

A novel approach to treatment of CP was developed in 1977, when the first human Total Pancreatectomy Islet Auto-Transplantation (TP-IAT) was performed at the University of Minnesota. The total pancreatectomy removes the source of the pain and theoretically eliminates risk of pancreatic cancer. In isolation, however, a total pancreatectomy would lead to a lifetime of brittle diabetes. The goal of the islet auto transplantation is to prevent or minimize TP-related diabetes. Isolated Islets of Langerhans are infused back into the patient most typically via the portal vein and eventually engraft in the sinusoids of the liver [19]. The first case report of pediatric TP-IAT was published by Wahoff et al. [20]. TP-IAT is now increasingly being used to treat children with chronic pancreatitis refractory to medical and endoscopic treatment. To date, case series specifically reporting on pediatric outcomes have been published by authors at the University of Minnesota Masonic Children's Hospital (n = 75), Cincinnati Children's Hospital (n = 14), and Children's Hospital of Pittsburgh of UPMC/Cleveland Clinic (n = 10) [21-23]. This review will describe the current experience specifically in reference to children.

Diagnosis of CP and Selection of Patients for TP-IAT

TP-IAT should be considered in children with refractory CP and impaired quality of life as indicated by inability to attend school or participate in ordinary activities [22]. Due to the extensive nature of the operation and the potential complication of lifelong diabetes, patients must be carefully selected to ensure that a TP-IAT will provide more benefit than harm. This is true of all patients undergoing workup for TP-IAT, but is of particular importance when considering a child. Reliable family support and treatment of mental health comorbidities are essential for successful post-operative outcomes in children [24].

The child should have an unequivocal diagnosis of chronic pancreatitis before receiving TP-IAT. At our institution, The Minnesota Criteria guide selection of appropriate patients [25]. Children must have abdominal pain for greater than 6 months' duration and objective findings of at least 1 major criterion or 2 minor criteria. *Major criteria* include pancreas calcifications on computed tomographic (CT) scan, abnormal endoscopic retrograde

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cholangiopancreatography (ERCP), a minimum of 6/9 standard criteria [26] on endoscopic ultrasound (EUS), histopathologically-confirmed CP (from previous resections), hereditary pancreatitis with compatible clinical history, or recurrent acute pancreatitis with > 3 episodes of pain accompanied by elevated serum amylase or lipase (> 3 times normal) and/or imaging diagnostic of acute pancreatitis. *Minor criteria* include ductal or parenchymal abnormalities on secretin-stimulated magnetic resonance cholangiopancreatography (MRCP), EUS of pancreas with 4/9 standard criteria, or abnormal pancreatic function tests with peak bicarbonate < 80 mmol/L.

Pre-operative evaluation of islet function should include fasting glucose, hemoglobin A1c, C-peptide levels, and oral or intravenous stimulatory tests [22,24]. Such measures may help estimate the likelihood of successful islet isolation [27,28].

Surgical Considerations in Pediatric Patients

Surgical technique is similar to adults except the vessels in the child are smaller and thus the surgeon must be diligent to avoid any inadvertent injury or spasm of the small vessels supplying the pancreas. The total pancreatectomy is done in such a way that the blood supply to the pancreas is preserved until just before its removal thus minimizing the warm ischemia time and maximizing the islet preservation. Gastrointestinal continuity can be restored by anastomosing in the first part of the duodenum to the fourth part of the duodenum with an end-to-side choledochoduodenostomy. Alternatively, a roux-en-y construction may be used using a 40 cm roux limb, an end-to-side choledochojejunostomy, and a duodenojejunostomy. A gastrojejunostomy tube is placed in the stomach using the Stamm technique and the tip of the jejunal tube placed in the distal jejunum. In all patients a cholecystectomy is done if not previously performed. Average operative time in published series is 8.9-9.8 hours [21,22].

Islet Isolation and Infusion

Pediatric pancreata present obstacles during islet isolation that differ from those of adults. Specifically, pancreata from young patients display a higher percentage islets embedded in acinar tissue after processing, known as of mantled islets [29,30]. To minimize the quantity of mantled islets, a prolonged enzymatic digestion is recommended prior to mechanical digestion. Enzymatic digestion is performed by intact class 1 (C1) and class 2 (C2) collagenases as well as neutral proteases, all from the organism *Clostridium histolyticum*. After ductal perfusion of the enzymes, the pancreas is digested using a modified Ricordi's semi-automated method [23,31]. The digested tissue is not typically purified for autologous transplantation unless volume reduction is required. Despite the small size of the pediatric pancreas, consistently high islet yield per gram pancreas can be obtained in children compared to adults [23,29,32]. Following isolation, the islet product is suspended in a Connaught Medical Research Laboratories (CMRL)-based media and returned to the operating room for infusion.

Pediatric patients have a smaller caliber portal vein and hence a higher degree of anticoagulation is needed during islet infusion to prevent thrombosis. The patient is typically given 70 units/kg of heparin, which is allowed to circulate for at least 3 minutes prior to islet infusion. The patient is also started on dextran 0.5 mL/kg per hour to a maximum of 10 mL/hr as a continuous infusion. Dextran specifically inhibits the extrinsic pathway of coagulation [33]. The islet preparation is infused by gravity into the portal vein system very slowly. At the author's institution, the total time spent on infusing islets in children can range from 60-110 min [21]. Portal pressures are monitored throughout the infusion. The infusion is stopped if the intraportal pressure exceeds 25 cm H_2O, the portal blood flow decreases to less than 100 ml/min, or the total tissue volume exceeds 0.25 ml/kg. Any remaining islet product is spread onto the peritoneum as a thin film.

Post-operative Care

Mean duration of hospitalization is 16-20.3 days [22,34]. Initially, patients are admitted to the intensive care unit (ICU) for post-operative monitoring, including frequent blood glucose checks [21,22]. A continuous infusion of insulin is adjusted to maintain blood glucose between 80 and 120 mg/dL. This is converted to subcutaneous insulin which is continued on discharge. Tube feeds are cycled and diet is advanced as gastric emptying improves. Tube feeds are stopped when the child can demonstrate adequate oral intake of calories and protein.

Regular use of digestive enzymes is required after total pancreatectomy. The target dose is 1500 lipase units/kg per meal and half this amount for snacks [21]. Patients also take fat-soluble vitamin supplementation (AquADEKs®) and are counseled to consume a low-oxalate diet to prevent kidney stones [35].

Nearly all pediatric patients receive exogenous insulin during the first three months post TP-IAT to relieve beta cell functional stress during the engraftment (neovascularization) stage [22,36-39]. During this time, islets rely on diffusion to obtain nutrients and oxygen and are particularly at risk of injury by hyperglycemia in an anoxic environment. Subsequently, insulin is gradually discontinued provided that blood glucose levels remain in a near normal target range. Target range is a fasting glucose of < 125 mg/dl, post-prandial glucose of < 180 mg/dl, and glycosylated hemoglobin ≤ 6.5% [25]. If these parameters are not met, then the patients must continue insulin use. Corticosteroids and other medications that induce hyperglycemia should be avoided whenever possible [40].

Splenectomy Management

Nearly all children who undergo TP-IAT will have their spleen removed as part of the procedure due to the technical difficulty of spleen preservation in this population and risk of post-operative splenic congestion [21,22]. Vaccination is completed at least 2 weeks pre-operatively and includes immunizations against Haemophilus influenzae type b, Meningococcus, and Pneumococcus. All children are maintained on prophylactic antibiotics for 1 year post-operatively [41]. This differs from adults, who do not undergo antibiotic prophylaxis following TP-IAT. Pediatric patients and their caretakers also receive counseling regarding the risks of infection following splenectomy and strategies for risk reduction.

Surgical Morbidity and Mortality

The operative mortality after TP-IAT in pediatric patients is very low (0-1%) [21-23]. In one series, surgical complications occurred in 15 (20%) of patients and including abdominal hemorrhage (5.3%), bowel obstruction (5.3%), abdominal abscess (4%), enteric leak (2.6%), biliary Leak (1.3%), and wound infection (1.3%) [21]. Of note, in this series, the complication rate was significantly lower in younger children < 12 years of age ($p = 0.041$). Interestingly, all 4 patients who developed intraabdominal bleeding had elevated islet infusion portal pressures (> 25 mm Hg). In another series, complications included acute respiratory distress syndrome, pneumonia, urinary tract infection, and central line-associated bloodstream infection [22]. None of the patients had long-term sequelae from their complications.

Post-splenectomy thrombocytosis (platelets count > 10^6/μL) occurs in 40% patients and is managed with hydroxyurea [21]. Although there is a risk of portal vein thrombosis with islet infusion, no pediatric cases have been reported thus far. Portal vein stenosis requiring a surgical shunt for correction has been reported in one patient [21].

Narcotic Use and Pain after TP-IAT

Prior to TP-IAT, pediatric patients required on average 32.7 mg morphine equivalents daily [22]. Following their operation, patients remain on narcotics for acute post-operative pain and the dose is gradually tapered. Narcotics can be discontinued in the majority of patients with 79-90% reported as narcotic-free on follow-up [21,22]. On post-operative surveys, patients report that pancreatitis-type pain and the severity of pain significantly improves over time ($p \leq 0.001$) following TP-IAT [21].

Islet Function after TP-IAT

In the largest series of pediatric patients to date, 41.3% achieved insulin independence following TP-IAT, and 90.3% of these patients did so within 1 year [21]. Younger children (< 12 years) are more likely to achieve insulin independence than older children (12-18) at a rate of 56.0% versus 40.5% (p = 0.05) [21]. In another series, 29% were insulin independent, and an additional 57% required less than 20 U/d of insulin daily [22]. Insulin independence has been observed for longer than 10 years after TP-IAT [21].

It is important to remember that without pancreatectomy, 30-50% of pediatric CP patients will develop diabetes in their lifetime solely from progression of their disease [18,42]. Also, even the children who have partial function and must use some insulin on a daily basis have been shown to have improved quality of life compared to their pre-TP-IAT status [21,34].

Factors Predicting Insulin Independence

There are several patient factors which are associated with a higher probability of insulin independence. These factors include younger age, lack of prior Puestow procedure, lower body surface area, higher IEQ/Kg body weight, and total IEQ transplanted [21-23]. Total IEQ given is by far the most strongly factor associated with insulin independence (OR = 2.62; p value < 0.001) [21]. Patients who received the most islets at > 5,000 IEQ/kg body weight fared best with insulin independence rate of 76% at 2 years post-op. This is in stark contrast to the 13% insulin independence rate of children who receive < 2,500 IEQ/kg [21].

Prior pancreatic surgery has been shown to have a significant impact on outcomes of TP-IAT. While previous surgery does not increase complication rates, drainage procedures such as the Puestow lead to significantly lower islet yields and increased the risk of insulin dependence [21,43]. It is important to counsel parents accordingly when considering a patient for TP-IAT post-surgical drainage procedures.

Health Related Quality of Life

The Medical Outcomes Study (MOS) 36-item Short Form (SF-36) Health Survey has been used to measure health-related quality of life (HRQOL) in pediatric patients having undergone TP-IAT [21,22,34,44-46]. The SF-36 measures a patient's individual health status in the form of a physical component summary (PCS) and the mental component summary (MCS) scores. The survey contains questions on physical functioning, role limitations attributed to physical and emotional health problems, bodily pain, general health, social functioning, vitality, and mental health [44-46].

Two institutions have studied HRQOL in pediatric TP-IAT patients. Results of these surveys show improvement in all tested modules following TP-IAT [21,22]. In particular, the physical component summary scale (PCS) score improved from pre-transplant by nearly 2 standard deviations (p value = 0.007) [21]. The Mental Component Summary Scale (MCS) similarly improved (p value = 0.024) [21]. The most dramatic improvements were seen in the categories of role limitations-physical (14 ± 7 at baseline vs. 83 ± 10 at 1 year, p < 0.001) and bodily pain (25 ± 5 at baseline vs. 70 ± 7 at 1 year, p < 0.001) [21].

At follow-up visits, children and their parents report integration back into their peer group, participation in extracurricular activities, and regular school attendance. In a survey of 30 patients and their patients (n = 30), 87% of respondents reported lost school days prior to TP-IAT [21]. By 2 years post TP-IAT, fewer than 5% or respondents reported lost school days. A separate survey of 7 patients showed return to full-time work or school in 5/7 patients while the remaining 2 patients declined to comment [22].

Conclusions

Chronic pancreatitis, though rare in children, is a debilitating disease that often leads to severe abdominal pain, pancreatic insufficiency, loss of school days, and narcotic dependence. Rare though it may be, pancreatitis is increasingly recognized as a cause of chronic abdominal pain in children [47]. Ongoing pain, such as that experienced by children with CP, has been associated with mental health issues such as anxiety, depression, low self-esteem, and also chronic physical health problems [48,49]. If medical or endoscopic interventions do not provide adequate relief for pediatric patients, a provider should consider total pancreatectomy to remove the root cause of the patient's pain.

With improvements in islet isolation, infusion, and engraftment, the complication of brittle diabetes can be avoided or minimized. As a rule, pediatric patients experience sustained pain relief and acceptable long-term glycemic control. Quality of life improves dramatically after TP-IAT, with most children reporting full-time return to school. Early referral to an experienced center allows for evaluation and surgical treatment before extensive damage to the pancreas has occurred. Further advances in islet isolation technique will allow increasing numbers of patients to remain insulin-independent.

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