

# Autologous Islet Transplantation After Pancreatic Resection Due to Trauma in a Toddler

A. Gill<sup>1</sup>, B. Dicken<sup>2</sup>, T. Kin<sup>3</sup>, D. O’Gorman<sup>3</sup>, E. Rosolowsky<sup>1</sup>, P. Senior<sup>3</sup>, M.D. Bellin<sup>4</sup>, A.M.J. Shapiro<sup>2,3</sup>, A.M. Haqq<sup>3</sup>

<sup>1</sup>Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada

<sup>2</sup>Division of General Surgery, University of Alberta, Edmonton, Alberta, Canada

<sup>3</sup>Clinical Islet Transplant Program and Alberta Diabetes Institute, University of Alberta, Edmonton, Alberta, Canada

<sup>4</sup>Schulze Diabetes Institute, Department of Surgery, University of Minnesota, Minneapolis, MN, USA

Corresponding Author: Andrea M. Haqq, MD, MHS, e-mail: andrea.haqq@albertahealthservices.ca

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## ABSTRACT

**Introduction:** Based on the available evidence, there appears to be a higher risk of onset of diabetes in patients post partial pancreatectomy. Autologous islet transplantation is currently offered selectively after total pancreatectomy for chronic pancreatitis and for benign pancreatic lesions. The indication for autologous islet transplantation has been expanded to avoid surgically-induced diabetes in post-traumatic pancreatic resections. Four such cases have been previously reported in the literature, all of which are adult patients.

**Case Report:** Following a motor-vehicle accident, pancreatic trauma occurred in a 3-year old boy. Partial jejunal resection and distal pancreatectomy with splenectomy were performed. The resected pancreas was processed and the isolated islets were infused into the liver. The patient maintained euglycemia at 3- and 10-months post-operatively.

**Conclusion:** We report the first pediatric case of autologous islet transplantation post partial pancreatectomy due to pancreatic trauma. It is evident from our case and other similar cases in adults that autologous islet transplantation may be performed safely after pancreatic trauma and surgical resection to reduce the risk of future onset of diabetes.

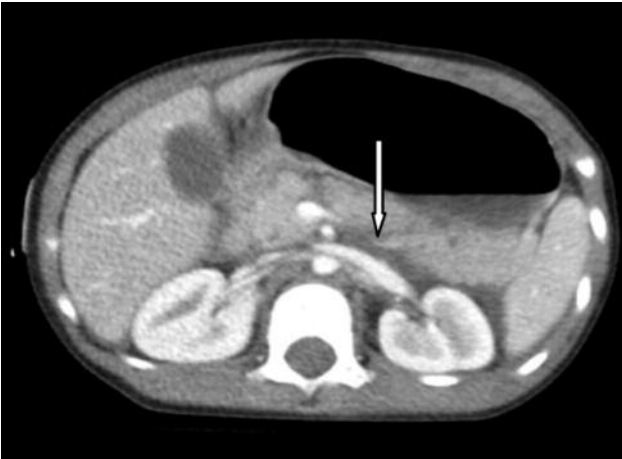
## CLINICAL REPORT

### INTRODUCTION

Approximately 10-20% of patients with distal pancreatectomy progress to diabetes in the absence of autologous islet transplantation<sup>1-4</sup>. Autologous islet transplantation has been performed in both adult and pediatric patients after pancreatectomy due to chronic pancreatitis<sup>2,5,6</sup>. Autologous islet transplantation after pancreatectomy for benign pancreatic tumors has also been reported<sup>1</sup>. To date, only four cases of autologous islet transplantation after pancreatic trauma and resection have been published<sup>4,7,8</sup>. We describe the first case of autologous islet transplantation post distal pancreatectomy for pancreatic trauma in a 3-year-old boy.

### CASE REPORT

A 3-year-old Caucasian boy was brought to the emergency room following a high-speed motor vehicle accident resulting in blunt abdominal trauma. He was previously healthy with no past medical history. There was no known family history of diabetes. A computed tomography (CT) image of the abdomen demonstrated a laceration of the third part of the duodenum and suspected incomplete laceration along the undersurface of the pancreatic neck and within the pancreatic tail (Figure 1). Extensive hemoperitoneum with shock bowel and a reduction in caliber of the aorta and inferior vena cava were noted. There was also an incomplete, small laceration along the medial surface of the spleen and suspected mesenteric hematoma.



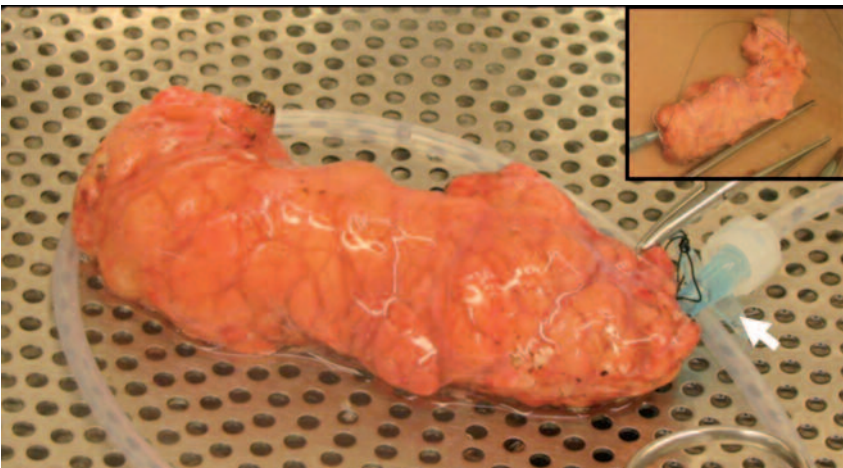
**Figure 1.** CT Abdomen of a 3-year old boy showing thoracic trauma incurred during a high-speed motor vehicle accident. Arrow indicates pancreatic laceration.

The patient was taken to the operating room for urgent laparotomy. Partial jejunal resection and distal pancreatectomy with splenectomy were performed. Given the extent of pancreatic resection required at the pancreatic neck, and the young age of this child, it was felt that an attempt to preserve pancreatic endocrine mass by autologous islet transplantation would be worthwhile. The resected pancreas was processed for islet isolation following a two hour cold ischemia time and stored in SPS-1 solution, in the Alberta Health Services' Clinical Islet Laboratory adjacent to the hospital. The pancreas (38.0 g) was perfused with collagenase blend solution via the main pancreatic duct (Figure 2) and digested for 10 minutes. The pancreatic digest [18 mL packed tissue volume (PTV) containing 239,390 islet equivalents (IEQ)] was subjected to a

purification process using a UW/Ficoll continuous density gradient to obtain an islet-enriched fraction and a less pure fraction. Both fractions were separately preserved in CMRL-1066 supplemented culture medium at 22°C (5%CO<sub>2</sub> and saturated humidity) while awaiting patient recovery.

Pre-operatively, serum glucose, insulin, c-peptide and glucagon concentrations were 6.9 mmol/L, 27 pmol/L, 0.41 nmol/L, and 20.7 ng/L, respectively. After a 48 hour postoperative period in the pediatric ICU, the patient was stable and underwent autologous islet transplantation by surgical access to the portal vein via the stump of the splenic vein. The islet-enriched fraction (2 mL PTV) and less pure fraction (7 mL PTV), together totaling 178,599 IEQ, were prepared for transplantation. The islet enriched fraction was infused into the liver through the portal vein without any significant rise in portal pressure. Subsequently, the less pure fraction was infused while portal pressure was carefully monitored. When portal pressure rose over 20 mmHg, the infusion was stopped. The remaining islets were not infused, but were assessed for quantity of islets, revealing 45,344 IEQ; a total of 133,255 IEQ (8,837 IEQ/kg body weight) were transplanted. The patient did not exhibit any complications related to the procedure and a subsequent Doppler ultrasound demonstrated patency of the portomesenteric system.

The patient initially received maintenance intravenous fluids and then parenteral nutrition after post-operative stabilization. As his gastrointestinal function improved, his diet was advanced from clear fluids to solid food over several days. The patient remained euglycemic throughout the entire hospitalization. Pancreatic enzymes were provided for exocrine insufficiency. The patient never required insulin during his hospital stay. He was discharged



**Figure 2.** The pancreas is distended uniformly through intra-ductal perfusion with collagenase blend solution. Arrow indicates a 22-gauge catheter inserted into the main pancreatic duct. Inset: the pancreas prior to distention.

home on pancreatic enzymes and aspirin (to reduce risk of thrombosis). Three months post-operatively the patient was euglycemic and HbA<sub>1c</sub> was normal at 5.6%. An oral glucose tolerance test (1.75 gram/kg glucose beverage) was carried out at this time, revealing normal insulin response (Table 1). A final OGTT was carried out 10 months post-operatively to assess the long-term success of the transplant and again showed a normal insulin response.

## DISCUSSION

This case and other similar cases highlight the potential role for autologous islet transplantation to prevent surgically-induced diabetes in patients undergoing pancreatectomy due to pancreatic trauma. Approximately 10-20% of patients with distal pancreatectomy progress to diabetes in the absence of autologous islet transplantation<sup>9-12</sup>. To our knowledge, this is the first case of successful autologous islet transplantation in a pediatric patient post distal pancreatectomy for pancreatic transection secondary to abdominal trauma. This is also the first report of islet transplantation in a child under the age of 5 years. Previous reports of pediatric islet transplantation have been in children at least 5 years of age who have undergone successful autologous islet transplantation after total pancreatectomy for chronic pancreatitis<sup>5</sup>.

The patient was euglycemic prior to islet transplantation. The rationale behind choosing to use the islets from his distal pancreas for transplant was to reduce the risk of development of diabetes later in life. At the time of islet transplantation, the remaining head, neck and uncinate process of his pancreas may indeed have been sufficient to maintain euglycemia but may have been insufficient to prevent the development of diabetes later in life. The incidence of development of diabetes in patients with distal pancreatectomy after pancreatic trauma in the pediatric population is not known with certainty. An incidence of diabetes of 16%

after pancreatic trauma has been reported, including patients who had distal pancreatectomy<sup>9</sup>. Other studies report an incidence of 7.5% to 36% of new-onset diabetes after distal pancreatectomy in the absence of trauma<sup>10-12</sup>. Rates are higher in patients with pre-existing pancreatic disease, especially chronic pancreatitis.

In the majority of cases, autologous islet transplantation after total pancreatectomy is performed immediately following pancreatectomy during the same surgical encounter. While islets are isolated, surgeons typically complete enteric and biliary reconstruction. In our case, the islet transplantation was not carried out during the initial surgery because the patient required time to stabilize after pancreatectomy, reconstruction procedures were not required, and the islet laboratory was not set up at the time of pancreatectomy because the emergency surgery took place late at night. Importantly for this young child, this period also allowed an opportunity for islet purification and culture to reduce the packed tissue volume and thereby reduce potential risk of portal thrombosis.

Despite its association with significant early loss of islet cells due to regional inflammatory responses, intrahepatic infusion of islet cells is standard practice in clinical islet transplantation protocols worldwide<sup>13</sup>. The shortcomings of hepatic engraftment have generated interest in investigating alternative transplant sites, particularly intramuscular<sup>14</sup> and subcutaneous<sup>15,16</sup> locations. However, use of these alternate sites remains experimental, and as no patient has been rendered insulin-free in the long-term by islet introduction at any extrahepatic site, the traditional introduction of islet cells via the portal vein was employed in the current patient.

Islet isolation from a pediatric pancreas is challenging as the majority of islets are trapped by a layer of mantled, exocrine tissue after digestion. We have performed 8 islet isolations from young de-

**Table I.** Results of oral glucose tolerance test in a 3-year old boy 3 months and 10 months after autologous islet transplant following pancreatectomy due to trauma.

Minutes	0		30		60		90		120	
	3	10	3	10	3	10	3	10	3	10
Time post-op (months)										
Insulin (pmol/L)	22	20	1036	247	172	148	87	130	188	101
Glucose (mmol/L)	4.3	7.4	9.2	6.8	6.5	6.6	5.0	6.6	6.5	6.0
C-peptide(nmol/L)	0.30	0.28	3.91	1.52	1.75	1.48	1.25	1.56	1.64	1.31

ceased donors (age 7 months to 12 years) over the last 15 years at the University of Alberta; 6 cases were not utilized for transplantation due to insufficient number of islets in a safe tissue volume. In the present case, PTV was 18 mL after digestion, which is far more than the recommended threshold volume (0.25 mL/kg body weight)<sup>17</sup>. Since impure islet preparations with high PTV carry an increased risk for portal vein thrombosis, we performed a purification procedure to reduce total tissue volume. Because 80% of the islets were trapped by a layer of exocrine tissue before purification, recovery of islets in the islet-enriched fraction was not sufficient (66, 354 IEQs in 2 mL PTV, 28% recovery). However, we circumvented this problem by also using the less pure fraction while carefully monitoring portal pressure. This may have been of benefit to the patient as it has been suggested that the presence of non-endocrine tissues may improve long-term survival and regenerative capacity of transplanted islets<sup>18</sup>. We were precluded from infusing no more than 40% of the less pure fraction (25% of total islets prepared) due to a rise in portal pressure. One approach to avoid this problem is to place the remaining islets into an alternate site, for example, the peritoneal cavity. A recent clinical study suggests that infusing remaining islets to an extrahepatic site, such as the peritoneal cavity, may be beneficial for hypoglycemic counterregulation, but it is also a fact that no subject has been rendered insulin independent through islet implantation in sites other than the liver<sup>19</sup>. We did not employ an alternate site because the patient had partial pancreatic head tissue remaining.

An ethical discussion of the merits versus the small risk of performing an islet cell transplant ensued in our case. A key point raised was that the medical risks of islet infusion to preserve beta cell mass after traumatic pancreatectomy are small because no immunosuppression is required. There is a small (4%) risk of portal thrombosis; therefore, total volume and portal pressures in the liver were limited. However, portal thrombosis in a child younger than 18 years of age has never been reported<sup>17</sup>. Further, while the influence of the islet transplant on glucagon response would certainly be of interest, it would be impossible to know whether any glucagon response to hypoglycemia was from transplanted or native alpha cells; the hypoglycemic challenge required to ascertain this information could not be justified in the patient.

As is evident from our case and other similar re-

ports, autologous islet transplantation after pancreatectomy in the setting of pancreatic trauma is a reasonable option, given that there is no need for immunosuppression, provided this can be accomplished with minimal risk of portal thrombosis. Clearly in this particular case, we cannot assign excellent glycemic control to the autologous islet transplant procedure alone, given the fact that the remnant head, neck and uncinate pancreas remain functional and intact. We have no way of knowing the relative contributions of the transplanted islet cells and the remnant endocrine tissue. However, this low-risk attempt to lower risk of lifelong diabetes makes intuitive sense and we recommend seizing the opportunity to preserve pancreatic endocrine mass through autologous transplantation in this setting, as a means to mitigate potential future risk of endocrine insufficiency. Further studies with long term follow up of these patients are required to establish the long term safety of autologous islet transplantation following pancreatic trauma and pancreatectomy in toddlers and young children.

#### CONFLICT OF INTERESTS:

The Authors declare that they have no conflict of interests.

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