Review

A Review of Autologous Islet Transplantation

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Autologous islet transplantation after total or semitotal pancreatectomy aims to preserve insulin secretory function and prevent the onset of diabetes. The major indication for pancreatectomy is chronic pancreatitis with severe abdominal pain, a benign pancreatic tumor, and trauma. The metabolic outcome of autologous islet transplantation is better than that of allogeneic transplantation and depends on the number of transplanted islets. Achieving islet isolation from a fibrous or damaged pancreas is one of the biggest challenges of autologous islet transplantation; a major complication is portal vein thrombosis after crude islet infusion. However, the incidence of portal vein thrombosis has decreased as islet preparation techniques have improved over time.

Key words: Total pancreatectomy; Islet; Autologous transplantation

INTRODUCTION

Autologous islet transplantation may prevent the onset of postoperative diabetes. Even if some exogenous insulin is required, diabetic control is simplified because the transplanted islets produce insulin in the long term. The major indication of pancreatectomy is chronic pancreatitis with severe abdominal pain. The first total pancreatectomy with autologous islet transplantation was carried out in 1977 at the University of Minnesota (28). Recently, some institutions have reported high numbers of autologous islet transplantation, including the University of Alberta (15 cases in 2012) (12), the University of South Carolina (33 cases in 2012) (19), the Baylor Research Institute (17 cases in 2010) (29), the University of Alabama (27 cases in 2009) (3), the University of Minnesota (86 cases in 2009) (2), the University of Leicester (46 cases in 2008) (32), and the University of Cincinnati (45 cases in 2005) (1). Here we review the current status of autologous islet transplantation.

Indications

Autologous islet transplantation is chiefly applied after a pancreatectomy to relieve pain due to chronic pancreatitis. However, the indications of total pancreatectomy are strict (5). The first step in managing pain due to chronic

pancreatitis is to confirm its diagnosis. The next step is to search for complications related to the diagnosis, including pancreatic cancer and gastroparesis, which should be treated first. Abstinence from tobacco and alcohol prior to and during the autologous islet transplantation process is essential (6). Medical therapy includes the use of nonsteroidal anti-inflammatory drugs, narcotic analgesic agents, antidepressant agents, and pancreatic enzymes. Endoscopic therapy, including ductal decompression, is limited to the dilated main pancreatic duct and requires the highest level of experience. The most commonly performed procedure for chronic pancreatitis with a dilated pancreatic duct is lateral pancreaticojejunostomy (27). A part of the pancreas is also resected. The final surgical component is total pancreatectomy with autologous islet transplantation.

Autologous islet transplantation is applied after partial pancreatectomy in cases of insulinoma (20), neuroendocrine tumors, and cystic neoplasms of the pancreas (11,23). We have also experienced two cases of autologous islet transplantation following a distal pancreatectomy. In these cases, tumors such as microcystic serous cystadenoma and intraductal papillary mucinous adenoma were present in the center of the pancreas; the tail part of the pancreas was digested and infused into the patient. In addition, autologous islet transplantation has been performed for trauma (10).

Islet Preparation and Transplantation

In cases of chronic pancreatitis, islet isolation is difficult because of the presence of fibrous tissue in pancreatic parenchyma. The method of islet isolation for autologous transplantation is not different from that for allogeneic transplantation. Islets are isolated using Ricordi's method (22) with modifications by each faculty. Collagenase, which is used to digest the pancreas, is a critical factor affecting isolation results. Liberase HI (Roche Diagnostics, Indianapolis, IN, USA) was widely used for clinical islet isolation for more than 10 years. However, this enzyme was disqualified from clinical use because of the potential risk of transmissible spongiform encephalopathy. Currently, the SERVA/Nordmark Collagenase NB1 and Neutral Protease NB Blend (SERVA Electrophoresis, Heidelberg, Germany) and Liberase MTF (mammalian tissue free) are used for clinical islet isolation (2,15). The development of new enzyme blends containing purified collagenases from *Clostridium histolyticum* and a neutral protease from *Bacillus thermoproteolyticus rokko* or *C. histolyticum* has also progressed (4).

Islets are generally transplanted into the portal vein immediately after isolation. Heparin is infused intravenously or with islet suspension to prevent clot formation around islets. Portal vein pressure is monitored during infusion. If portal hypertension (>25 – 28 mm H₂O) is observed, infusion into the portal vein is abandoned, and the remaining islets are transplanted into other sites.

Preventing hyperglycemia during the operative period is important because it can damage islet cells as a result of islet exhaustion (24). Hyperglycemia is reported to decrease blood flow in the transplanted islets and inhibit their vascularization (7). Glucose-containing solutions should not be administered to patients before islet cell infusion. Moreover, IV exogenous insulin administration is essential after transplantation (14).

Complications

Portal vein thrombosis can occur after autologous islet transplantation. The Leicester group reported their experiences with 24 patients who underwent this process (33), in which one patient (4.2%) developed portal vein thrombosis and was subsequently treated with anticoagulant therapy. The University of Cincinnati group reported portal vein thrombosis in 1 (0.9%) of 107 cases (30) that was treated with a combination of mechanical thrombectomy and thrombolytics. The Baylor group reported that major portal vein thrombosis with radiological intervention was required in 1 (3.8%) of 26 autologous islet transplantation procedures (15). The University of Minnesota (31) and University of Alabama (3) groups have reported 48 and 26 cases of autologous islet transplantation, respectively; neither group reported any patient who developed portal vein thrombosis. The crude preparation increased

thrombogenicity due to elevated thromboplastin activity (8,30). The University of Alberta group reported that nonpurified islet autologous transplantation increases the risk of acute portal hypertension compared to allogeneic islet transplantation; in addition, they have reported that portal hypertension is associated with the packed cell volume and number of transplanted cells (12).

Several cases of disseminated intravascular coagulation (DIC) after transplantation have been reported (8,16). Severe postoperative hemorrhage was observed in some cases. The presence of tissue factor from the mincing of the pancreas is suggested to be an initiating factor for the development of thrombosis and DIC. Heparin is infused before autologous islet transplantation to prevent clot formation. One case of heparin-induced thrombocytopenia has been reported (21). The incidence of portal vein thrombosis has decreased over time as the technique of islet preparation has improved.

Postoperative infectious complications require attention because pancreatic fluid is frequently reported to be infected (18). The University of Cincinnati group reported that 25 (89.3%) of 28 patients had bacterial culture-positive media solution (transport or transplantation solution); however, only four (14.3%) patients had an infectious complication (35).

The Leicester group reported splenic infarction after spleen-preserved total pancreatectomy and autologous islet transplantation into the spleen (34). They mention that if the splenic artery and vein are ligated, the spleen should be used for islet transplantation with caution.

Transplantation Site

Most programs apply intraportal infusion to the liver because of its large capacity to receive transplanted islets as well as the relative ease of transplantation with minimal side effects. However, the liver may not be the optimal transplantation site (25,26). The liver presents unstable environments for the islets including variable oxygen availability and angiogenic activity. Postprandial hyperglycemia in the liver may affect islet β -cells. Insulin and glucagon from the islets transplanted in the liver drain into the systemic vein and not into the portal vein. The spleen and intra-abdominal cavity, especially the omental pouch, are suggested to be optimal autologous islet transplantation sites (9). Theoretically, the spleen provides an environment similar to the native pancreas for the transplanted islets. Moreover, insulin naturally drains into the portal vein. However, as described above, islet transplantation into the spleen confers risks of splenic infarction and portal vein thrombosis. The intraperitoneal and omental pouch sites are suitable for transplanting unpurified autologous islets because they do not limit the amount of transplanted tissue (13). Furthermore, the omentum has a relatively high blood content and a number

of blood vessels, which increases the vascular supply to the transplanted islets. However, a large number of islets are required to actually reverse hyperglycemia (17).

At present, comparatively pure islets should be transplanted via the portal vein while monitoring the portal vein pressure; if the portal vein pressure is elevated, relatively crude islets should be transplanted into the omental pouch.

Metabolic Outcome

The University of Minnesota, University of Alabama, University of Cincinnati, and University of Leicester have reported on the metabolic outcomes of autologous islet transplantation. The Minnesota group used two different enzyme blends: Liberase HI (LH) and SERVA/Nordmark (SN). In the LH group ($n=33$), 5 patients (15%) were insulin independent, 21 (64%) had partial function, and 7 had graft failure. In the SN group ($n=26$), 6 patients (23%) were insulin independent, 19 (73%) had partial function, and 1 had graft failure. If $>5,000$ IEQ/kg islets were transplanted, the probability of graft function was 100% (2). The Alabama group reported that insulin independence was not achieved in any of their patients ($n=27$); however, the total number of transplanted islets was very low ($1,331 \pm 304$ IEQ/kg, mean $\pm$ SEM) (3). Meanwhile, the Cincinnati group divided 45 patients into insulin-dependent (27 patients, 60%) and insulin-independent (18 patients, 40%) groups. The number of transplanted islets was significantly greater in the insulin-independent group than in the insulin-dependent group ($6,635 \pm 229$ vs. $3,799 \pm 629$). Interestingly, only 1 of 15 male patients achieved insulin independence, in contrast to 17 of 30 female patients. The authors reported that the possible reason of higher islet yields in women was that they were 10 kg lighter than men, on average (1). The Leicester group reported the long-term assessment of graft function. Twelve of 46 patients (26%) showed periods of insulin independence for 2–63 months. Over a 10-year follow-up period, notable increases in insulin requirements and the percentage of glycosylated hemoglobin levels were observed. However, all tested patients were C-peptide positive, and high fasting and stimulated C-peptide values were recorded 10 years after transplantation (32).

CONCLUSIONS

Total pancreatectomy may provide pain relief for patients with chronic pancreatitis when other therapies have failed. Autologous islet transplantation is performed to prevent or minimize postsurgical diabetes. In addition, it is performed after total or partial pancreatectomy for benign pancreatic tumors and trauma. The major complication is portal hypertension and portal thrombosis. Improvements in islet preparation have decreased the incidence of portal vein thrombosis.

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