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FULL PAPER

Single-centre experience of extending indications for percutaneous intraportal islet autotransplantation (PIPIAT) after pancreatic surgery to prevent diabetes: feasibility, radiological aspects, complications and clinical outcome

¹MASSIMO VENTURINI, MD, ¹CLAUDIO SALLEMI, MD, ¹CATERINA COLANTONI, MD, ¹GIULIA AGOSTINI, MD, ²GIANPAOLO BALZANO, MD, ^{1,3}ANTONIO ESPOSITO, MD, ^{3,4}ANTONIO SECCHI, MD, ^{1,3}FRANCESCO DE COBELLI, MD, ^{2,3}MASSIMO FALCONI, MD, ⁵LORENZO PIEMONTE, MD, ⁴PAOLA MAFFI, MD and ^{1,3}ALESSANDRO DEL MASCHIO, MD

¹Department of Radiology, San Raffaele Scientific Institute, Milan, Italy

²Department of Pancreatic Surgery, San Raffaele Scientific Institute, Milan, Italy

³Vita-Salute University, San Raffaele Hospital, Milan, Italy

⁴Department of Internal Medicine, Transplant Unit, San Raffaele Scientific Institute, Milan, Italy

⁵Diabetes Research Institute, San Raffaele Scientific Institute, Milan, Italy

Address correspondence to: Dr Massimo Venturini

E-mail: venturini.massimo@hsr.it

Objective: Islet allotransplantation is a less invasive alternative to surgical pancreas transplantation for Type 1 diabetes, while percutaneous intraportal islet autotransplantation (PIPIAT) is usually performed after pancreatic surgery to prevent diabetes. Our aim was to assess the feasibility, radiological aspects, complications and clinical outcome of PIPIAT following pancreatic surgery for not only chronic pancreatitis but also benign and malignant nodules.

Methods: From 2008 to 2012, 41 patients were enrolled for PIPIAT 12–48 h after pancreatic surgery (extended pancreatic surgery for chronic pancreatitis and benign/malignant neoplasms). PIPIAT was performed using a combined ultrasonography and fluoroscopy-guided technique (4-F catheter). PIPIAT feasibility, median follow-up and metabolic (insulin independence rate, graft function based on C-peptide levels) and oncologic outcomes were recorded.

Results: PIPIAT was not performed in 7/41 patients (4 cases for an inadequate islet mass, 2 cases for

haemodynamic instability and 1 case for islet culture contamination), while it was successfully performed in 34/34 patients. Procedure-related major complications occurred in four patients: two bleedings requiring transfusions, one patient with left portal vein thrombosis and one patient with sepsis. Median follow-up duration was 546 days. Insulin independence was achieved in 15/34 (44%) patients, partial graft function in 16/34 (47%) patients and no function in 3/34 (9%) patients. None of the 17 patients with malignant nodules developed liver metastases during follow-up.

Conclusion: PIPIAT, performed under ultrasound and fluoroscopy combined guidance and not requiring immunosuppression, is feasible, with a relatively low complication rate and a better metabolic outcome than allotransplantation.

Advances in knowledge: PIPIAT can prevent pancreatogenic diabetes. Ultrasound is a useful tool for the guidance and monitoring of PIPIAT.

INTRODUCTION

Combined kidney/pancreas transplantation represents the treatment of choice in patients affected by long-term Type 1 diabetes and chronic renal insufficiency.^{1,2} However, percutaneous intraportal islet transplantation from cadaveric donors (allotransplantation), because of the biological replication of beta cells in the liver, represents a valid alternative to surgical pancreas transplantation for Type 1 diabetes, being a less invasive, feasible and reproducible procedure.³

Since the 1990s, islet after kidney transplantation has represented a good therapeutic option to treat diabetes associated with chronic renal failure⁴ in case of pancreas unavailability from a cadaveric donor at the time of kidney transplantation. Since the 2000s, with the establishment of the Edmonton Protocol,⁵ islet transplantation alone is performed in patients affected by brittle, Type 1 diabetes with preserved renal function, based on the infusion of a large islet mass and on a glucocorticoid-free immunosuppressive regimen, aiming to obtain insulin

independence or a significant reduction of exogenous insulin requirement; the aim is to prevent hypoglycaemic episodes and diabetic complications^{6,7} such as nephropathy⁸ or retinopathy⁹ and to ameliorate the life expectancy.¹⁰ Another type of diabetes is known as “pancreatogenic diabetes”, an extreme disruption of glucose homeostasis caused by the loss of parenchyma after pancreatic resection such as total/subtotal pancreatectomy for chronic pancreatitis or tumours.^{11,12} The percentage of patients undergoing pancreatectomy that develop pancreatogenic diabetes is 8–23% increasing up to 40–50% during the follow-up;^{13,14} pancreatogenic diabetes can be prevented by percutaneous intraportal islet autotransplantation (PIPIAT), which is performed 12–48 h after surgery, does not require immunosuppression and has a lower rejection rate than allotransplantation.¹⁵ The technical procedure of autotransplantation, as in allotransplantation, consists in isolation, centrifugation and percutaneous intraportal infusion of pancreatic islets, performed using a combined ultrasonographic and fluoroscopic guidance,¹⁶ to reduce peri-procedural complications. The aim of our study was to evaluate the feasibility, radiological aspects, complications and clinical outcome of PIPIAT after pancreatic surgery in patients affected by chronic pancreatitis or benign or malignant tumours.

METHODS AND MATERIALS

Population

From 2008 to 2012, patients referring to our pancreatic surgery department affected by pancreatic diseases were assessed and considered as potential candidates for PIPIAT, according to the following conditions: (1) if they had painful chronic pancreatitis without cephalic masses; (2) if they had major complications after pancreatic surgery such as Grade C pancreatic fistula¹⁷ requiring relaparotomy with complete pancreatectomy or left pancreatectomy; (3) if they were undergoing pancreaticoduodenectomy with a high risk of anastomotic leakage, based on a combination of a narrow duct and a soft/frail pancreatic texture; and (4) if they were undergoing extensive distal pancreatectomy for benign/borderline tumours located at the level of the body/neck.

Pre-operatively, all patients were assessed by abdominal colour-Doppler ultrasound to evaluate the patency and regular blood flow direction of the portal vein and liver echotexture (ATL-Philips IU-22; Philips Healthcare, Bothell, WA). The appearance of liver steatosis during follow-up has been considered as an early predictor of graft dysfunction.^{18,19}

Eligibility for PIPIAT was based on the following criteria: >18 years of age, written informed consent and fasting glycaemia of $<126 \text{ mg dl}^{-1}$ without glucose-lowering medications. Pancreatic malignant disease was not considered as an absolute exclusion criterion, while exclusion criteria considered were the following conditions: (1) multifocal pancreatic neoplasm at pre-operative imaging or intraoperative evaluation, including multifocal benign intraductal papillary mucinous neoplasm; (2) suspected or confirmed diagnosis of multiple endocrine neoplasms; (3) transection margin involvement in the pancreatic pathology, including any degree of dysplasia or ductal disepithelization; and (4) any medical condition potentially compromising the safety of the PIPIAT procedure.

All patients were submitted for deep vein thrombosis prophylaxis based on low molecular weight heparin (4000 IU/day from Day 0–Day 28). Local ethical committee approval was obtained for the assessment and transplantation follow-up study, and all patients signed informed consent.

Islet preparation

Open or laparoscopic surgery was performed under general anaesthesia. If a tumour was the reason for pancreatic resection, 1 cm of the pancreatic remnant proximal to the pancreatic margin was resected and sent for frozen section examination to confirm margin negativity.

The pancreatic tissue was immediately flushed with the cold University of Wisconsin preservation solution at 4 °C until the process of isolating the pancreatic islet cells was begun at the Islet Processing Facility of our hospital (cold ischaemia time, 3–8 h).

Islets were isolated and purified according to the automated method described by Ricordi et al:²⁰ briefly, the pancreatic duct was cannulated with a 14–20-G catheter and perfused by a collagenase solution. After parenchymal distension, the organ was digested and the islets were freed from the exocrine tissue. Using a COBE® machine (Terumo BCT, Inc., Lakewood, CO), the islets were then purified.

Pancreatic islet preparation was considered adequate for transplantation, according to the following criteria: (a) the presence of sterility, defined as the absence of aerobic and anaerobic bacteria, fungi and mycoplasma; (b) the presence of >6000 equivalent islets (IEQ) per kilogram body weight, determined with islet volume and insulin content measurements in 100-l aliquots of preparation (quantification of pancreatic islets was performed in IEQ to account for variations in the cell volume, with an average standard pancreatic islet diameter of 150 µm, as previously described by Ricordi et al;²¹ the actual number of islets was finally calculated); (c) purity >20%, determined with morphometric analysis and with the ratio obtained by dividing the estimated islet mass by the total mass of the preparation; and

Figure 1. Ultrasound-guided percutaneous transhepatic portal vein puncture: a peripheral branch of the right portal vein is punctured under ultrasonographic guidance.

(d) islet viability, assessed with propidium iodide stain. Mean pancreas weight, pre- and post-purification median IEQ number and IEQ number isolated per gram of pancreas pre- and post-purification were assessed. Percentage of preparations considered adequate for PIPIAT was also calculated.

Percutaneous intraportal islet autotransplantation procedure

PIPIAT was performed 12–48 h after islet isolation, according to the protocol approved by the institutional review board. All the procedures were performed in an angiographic suite using a combined ultrasonographic and fluoroscopic guidance.¹⁶ An ultrasound colour-Doppler unit (HDI 5000; ATL-Philips Medical Systems, Bothell, WA) was used for ultrasonographic guidance during right portal vein puncture (Figure 1) with a 22-G needle by using a right-sided intercostal approach and local anaesthesia, as previously reported.¹⁶

Fluoroscopic guidance was used to perform main trunk portal vein catheterization as follows: a 0.018-inch guide wire was advanced through the needle into the main portal vein and a straight end-hole 4-F catheter was positioned over the guide wire. About 150 ml of a preparation containing 300,000–800,000 purified pancreatic islets in suspension was slowly injected (20–30 min) *via* the catheter. In addition, 1500–2000 IU of heparin was infused into the portal vein with the islet suspension. A slow injection is important to avoid possible rupture of islets within the catheter. Portography (Figure 2) and portal vein pressure (PVP) measurement were performed before and after the infusion of pancreatic islets. At the end of the procedure, the catheter was slowly retracted and intrahepatic tract embolization was performed using gelatin sponge pledgets. Enoxaparin, 6000 IU d⁻¹, was administered subcutaneously for 7 days after the procedure.

Percutaneous intraportal islet autotransplantation monitoring

Immediately after the PIPIAT procedure (and at 1, 3 and 7 days thereafter), patients were examined with colour-Doppler ultrasound

Figure 2. Percutaneous transhepatic portography before percutaneous intraportal islet autotransplantation: portography shows catheterization of the main trunk of the portal vein, with regular patency and flow of the main portal branches.

for signs of bleeding or thrombosis (e.g. fluid collection around the liver or absence of flow into the portal vein, respectively) and eventually, they were examined with contrast-enhanced multi-detector CT also. Colour-Doppler ultrasound examination was repeated at 1, 6 and 12 months and every year thereafter to evaluate portal vein patency and hepatic steatosis appearance.

Beta-cell function was assessed, as for islet allotransplantation, by the measurement of fasting C-peptide (defined as positive for levels ≥ 0.3 ng ml⁻¹), glycated haemoglobin, glycaemia and average daily insulin requirements. According to Luzi's classification,²² islet function was also defined as follows: full function (insulin independence), partial function (C-peptide > 0.5 ng ml⁻¹) and no function (C-peptide < 0.5 ng ml⁻¹).

In case of malignancy, a contrast-enhanced multidetector CT scan (Philips Brilliance 64®, Philips Medical Systems Inc., Cleveland, OH) and blood neoplastic markers were performed every 3 or 6 months, according to the risk of recurrence.

Statistical analysis

All statistical analyses were performed using SPSS® v. 13.0 statistical software (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL). Data are presented as mean $\pm$ standard error of the mean or median (range) as appropriate. Continuous variables were compared with Student's *t*-test (variables with a normal distribution) or Wilcoxon signed-rank test (variables with a non-normal distribution). Univariate and multivariate Cox's proportional hazard regression analyses were performed.

All tests were conducted using an α level of 0.05 to indicate statistical significance.

RESULTS

41 patients were enrolled for PIPIAT (12 patients with periampullary tumours, 9 patients with adenocarcinomas, 8 patients with cystic neoplasms, 7 patients with neuroendocrine neoplasms, 3 patients with chronic pancreatitis and 2 patients with gastrointestinal stromal tumour) after pancreatic surgery.

Indications for PIPIAT were as follows: (1) 2 patients underwent subtotal pancreatectomy for chronic pancreatitis; (2) 15 patients underwent relaparotomy for Grade C pancreatic fistula: in 13 patients, complete pancreatectomy was performed because of a leakage of the pancreatic anastomosis after pancreaticoduodenectomy, whereas in 2 patients, distal pancreatectomy was performed because of main duct disruption following enucleation; (3) 16 patients initially scheduled for pancreaticoduodenectomy were actually submitted for total pancreatectomy; and (4) 8 patients underwent extensive distal pancreatectomy for neoplasms located at the pancreatic body/neck.

The mean pancreas weight was 59.1 ± 3.29 g. The median pre-purification and post-purification number of islets were 152,266 IEQ (0–349,000 IEQ) and 151,400 IEQ (0–335,950 IEQ) ($p = 0.01$), respectively. Thus, the median number of IEQ isolated per gram of pancreas was 2964 IEQ (0–6536 IEQ) pre-purification and 2190 IEQ (0–5380 IEQ) post-purification

($p = 0.015$). Eventually, 34/41 (83%) patients were submitted for PIPIAT.

5 (12.2%) of 41 islet preparations were considered inadequate for transplantation owing to a low islet number (IEQ/kg < 50 , $n = 4$) or bacterial contamination ($n = 1$). 2 (4.9%) patients could not undergo transplantation because of a critical clinical condition: one patient had a cardiac arrest owing to malignant arrhythmia during surgery after pancreas resection and the other patient was haemodynamically unstable owing to massive haemobilia requiring angiographic embolization owing to a previous percutaneous biliary drainage for a biliary fistula.

Procedure-related complications occurred in 8 (23.5%) of 34 patients: 4 major complications and 4 minor complications. Specifically, portal vein thrombosis, not recorded at portography post-transplant but during the colour-Doppler ultrasound follow-up, occurred in three patients (one patient with left portal vein thrombosis and two patients with segmental thrombosis). All these patients were successfully treated with anticoagulation therapy based on low molecular weight heparin. Four patients experienced bleeding: in two cases, the bleeding did not require intervention (ultrasound-detected small perihaptic fluid collections) and in two cases, it required transfusion alone. Finally, sepsis (*Staphylococcus haemolyticus* and *Enterococcus faecalis* bacteraemia) requiring long-term antibiotics treatment occurred in one patient.

A statistically significant increase ($p < 0.001$) in the PVP occurred after islet infusion (pre-infusion PVP 12.1 ± 0.74 cm H₂O; post-infusion PVP 13.5 ± 0.88 cm H₂O).

At follow-up ultrasound, hepatic steatosis was found in only one patient 6 months after PIPIAT (Figure 3) and disappeared 12 months after; in this patient, the islet graft was unsuccessful, with C-peptide values < 0.3 ng ml⁻¹.

15 (44%) of 34 patients reached insulin independence, 16 (47%) patients had partial graft function and 3 (9%) patients

experienced graft loss. 15 patients who obtained insulin independence maintained it for more than 3 months (21 months as median) with full graft function: in 3/15 patients, insulin independence was lost within 1 year. The gain of insulin independence was associated with the number of infused islets, extent of pancreatectomy and diagnosis of benign diseases.

The multivariate Cox's proportional hazard regression model confirmed islet number (hazard ratio: 1.701, 95% confidence interval: 1.05–2.76; $p = 0.032$) and partial pancreatectomy (hazard ratio: 5.24, 95% confidence interval: 1.27–21.6; $p = 0.022$) as independent risk factors for insulin independence.

Median follow-up was 546 days (range 89–1254 days).

No patient with a malignant pancreatic tumour developed metastasis during follow-up.

DISCUSSION

PIPIAT to prevent pancreatogenic diabetes after pancreatic surgery is performed in an angiographic suite, as in the case of allotransplantation, from a cadaveric donor to cure Type 1 diabetes: at our centre, ultrasound is used as real-time guidance of portal vein puncture, associated with the conventional fluoroscopic guidance to catheterize the portal vein.¹⁶ Ultrasound guidance allows reducing the number of puncture attempts, transplantation mean time and procedure-related complications. Procedure-related complications are most frequently bleeding and portal vein thrombosis. Comparing the three islet-transplanted populations, patients with islet-alone allotransplantation present a lower theoretical bleeding risk than patients with kidney-islet allotransplantation and islet autotransplantation, submitted for chronic aspirin and anticoagulation treatment, respectively.

Usually, patients considered for PIPIAT undergo procedure 12–48 h after pancreatic surgery: this peculiar situation may cause haemodynamic instability and a suboptimal ultrasound visibility that may hinder the procedure. However, the real fundamental difference between patients with allotransplantation and those with autotransplantation is that immunosuppressive treatment is not required in patients with autotransplantation: for this reason, the rejection rate is almost null and the clinical outcome is better.¹¹ Beyond the different purposes of allotransplantation and autotransplantation (cure vs prevention of diabetes), the common goal is to improve the patient quality of life, to reach insulin independence or to significantly reduce exogenous insulin requirement^{23–25} and to prevent diabetes-related complications, such as nephropathy, retinopathy and neuropathy.^{8,9,26} The recent increase in the number of PIPIAT can be correlated to the increase in the number of patients considered for major pancreatic surgery, a prerogative of high-volume medical centres,²⁷ and the early diagnosis of pre-malignant lesions because of the improvement of diagnostic tools.²⁸ The surgical resection of the pancreatic parenchyma induces an acute instability of the glucose haemostasis, known as “pancreatogenic diabetes”,²⁹ characterized by an alternation of hypoglycaemic and hyperglycaemic episodes, with a great impact on the quality of life and life expectancy. PIPIAT, an effective approach for the prevention of pancreatogenic diabetes, was

Figure 3. Ultrasonographic examination performed 6 months after percutaneous intraportal islet autotransplantation: multiple hyperechoic micronodules (arrows) referable to multifocal hepatic steatosis are evident.

first performed in 1977³⁰ and, in the beginning, only in patients submitted for pancreatic surgery for chronic pancreatitis.³¹ Recently, the clinical indication of PIPIAT has been extended to the loss of pancreatic parenchyma for benign and low-grade malignant pancreatic tumours³² and after abdominal trauma.³³

Until now, in patients with pancreatic malignancy, this procedure was limited owing to the concern of infusing occult carcinoma cells inside the islet preparation. In the same way, PIPIAT was limited in patients affected by life-threatening leakage of pancreatic jejunostomy owing to the fear of spreading infection.

In the present study, the extension of the enrolment criteria allowed the inclusion of patients with these two medical conditions, which increased risk of procedural complications. In our experience, no liver metastasis was recorded during the oncologic follow-up of 17 patients affected by malignant neoplasms and submitted for PIPIAT. Only multifocal intraductal papillary mucinous neoplasm has been considered as an exclusion criterion for PIPIAT, because multicentricity of cancer is thought to improve the risk of disseminating an unrecognized malignant tumour to the liver. Disseminating infection represents an additional potential risk of PIPIAT. In our series, considering patients with or without leakage of the pancreatic jejunostomy separately, an actual positivization at microbiological sterility test within 5 days was recorded in 83% and 13% of the cases, respectively: this finding suggests that bacterial contamination of the dispersed pancreatic tissue is relatively common. However, only one patient developed infection by the same bacteria isolated in the culture of infused islets; therefore, we can assume that the clinical risk of bacterial infection in PIPIAT is very low, also owing to sterile manoeuvres adopted during tissue centrifugation and the routine use of antibiotics.

In our study, procedure-related complications were recorded in 8/34 (23.5%) patients, but only 4 (11.7%) patients experienced major complications, all resolved conservatively: 1 case of sepsis, 1 case of left portal vein thrombosis, both successfully treated with antibiotic and anticoagulation therapy, respectively, and 2 cases of bleeding, both resolved with transfusion alone (not embolization or relaparotomy). The use of ultrasonographic guidance and the embolization of the intrahepatic tract are important to reduce the liver puncture attempts and the risk of bleeding, respectively. The relatively high percentage of bleeding is probably related to the kind of patients enrolled: patients submitted for major surgery and under anticoagulant treatment were patients with higher risk of bleeding during PIPAT.

As previously reported,³⁴ and also in our series, a moderate increase of PVP was recorded after PIPIAT: this finding, often recorded after islet transplant, was already demonstrated to be strictly correlated to the number/volume of infused islets and the number of transplant procedures.³⁵ PVP increase is usually lower in autotransplantation than in allotransplantation, during which a higher islet mass is usually infused.⁵ Furthermore, islet autotransplantation is performed only once, while islet allotransplantation may require repeat procedures (two or three) for the maintenance of insulin independence or a significant reduction of exogenous insulin requirement, with higher increase of PVP.

As concerns the metabolic outcome, our study demonstrates how PIPIAT can achieve good results in a relatively short follow-up (546 days): insulin independence was obtained in 15/34 (44%) patients, which was maintained for more than 3 months (21 months as median) with full islet graft function; the reduction in glycated haemoglobin, fasting C-peptide levels ($>0.5 \text{ ng ml}^{-1}$) and the reduction of exogenous insulin during follow-up were markers of a good graft function.

Partial graft function was achieved in 16/34 (47%) patients. Fasting C-peptide levels, even if partial or short, have been considered as an important goal, because they were demonstrated to have an important role in the prevention of diabetic complications¹⁰ and for lipid and protein homeostasis.

In our opinion, best clinical results were correlated to a great quantity of islet infused and to the kind of surgery, in particular to partial pancreatectomy, resulting as independent predictors of metabolic outcome. Graft loss was registered in a low percentage of patients [3/34 (9%) patients] with C-peptide levels $<0.3 \text{ ng ml}^{-1}$; 1 among these patients showed hepatic steatosis 6 months after PIPIAT, disappearing 6 months later. The role of imaging in islet transplantation^{36,37} and particularly in the presence of hepatic steatosis at ultrasound or MRI after pancreatic islet transplantation has been a concern of debate:^{38–40} some authors relate this phenomenon to the lipogenic action of pancreatic cells without any specific correlation to graft function;^{38,39} conversely, the authors of the present study consider hepatic steatosis as an early marker of graft dysfunction.¹⁸ This hypothesis is also supported by the evidence that patients with autotransplantation, which is demonstrated to achieve a better clinical outcome, register a lower percentage of hepatic steatosis than patients with allotransplantation. The detection of steatosis at ultrasound has been interpreted as a consequence of an islet-overworking activity owing to residual-stressed vital islets in insulin overproduction supporting other non-functioning islets: we have hypothesized that steatosis becomes ultrasonically detectable only when a significant peak of local insulin secretion is achieved.¹⁹ An islet-overworking activity was previously demonstrated in some patients in whom transplantation failed.⁴¹

In conclusion, the present study confirms that PIPIAT could be extended to different categories of patients, in centres experienced in islet transplantation and characterized by high-volume pancreatic surgery. PIPIAT can help prevent pancreatogenic diabetes, improving the patient quality of life and minimizing diabetic-related complications. Considering the radiological aspects, the use of a combined ultrasonographic and fluoroscopic guidance in both islet autotransplantation and islet allotransplantation can be considered a safer procedure than using fluoroscopic guidance alone. Colour-Doppler ultrasound can be useful as not only a guidance for the procedure but also a simple, non-invasive tool for the monitoring of PIPIAT: in the immediate follow-up to quickly diagnosing periprocedural complications (bleeding, thrombosis) and in the mid- and long-term follow-up to assess hepatic steatosis appearance, interpreted as an early marker of graft dysfunction.

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