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REVIEW ARTICLE

Current status of total pancreatectomy with islet autotransplantation for chronic and recurrent acute pancreatitis

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Abstract

Total pancreatectomy with islet autotransplantation (TPIAT) is an established and effective treatment modality for patients diagnosed with intractable chronic pancreatitis (CP) and recurrent acute pancreatitis (RAP). TPIAT primarily aims to manage debilitating pain leading to impaired quality of life among patients with CP or RAP, which can be successfully managed with medical, endoscopic, or surgical interventions. TPIAT is significantly successful in relieving pain associated with CP and improving health-related quality of life outcomes. Furthermore, the complete loss of pancreatic endocrine function attributed to total pancreatectomy (TP) can be compensated by autologous islet transplantation (IAT). Patients receiving IAT can achieve insulin independence or can be less dependent on exogenous insulin compared with those receiving TP alone. Historically, TPIAT has been mainly used in the United States, and its outcomes have been improving due to technological advancements. Despite some challenges, TPIAT can be a promising treatment for patients with CP-related intractable pain. Thus far, TPIAT is not commonly performed in Japan. Nevertheless, it may improve health-related quality of life in Japanese patients with CP, similar to Western patients. This review article aimed to provide an overview of the indications, related procedures, and outcomes of TPIAT and to discuss future prospects in Japan.

KEYWORDS
autologous transplantation, chronic pancreatitis, islet transplantation, pancreatectomy, quality of life

1 | INTRODUCTION

Chronic pancreatitis (CP) is characterized by pathological fibro-inflammatory syndrome of the pancreas based on the recently proposed mechanistic definition.[1] This condition primarily affects individuals who possess genetic, environmental, and/or other risk factors, leading to persistent pathological responses in the pancreatic tissue caused by injury or stress.[1,2] CP causes such severe pain often requiring opioid treatment, which significantly diminishes the overall quality of life (QoL).[3,4] To reduce pain and improve QoL, surgical treatment is considered for patients with CP or recurrent acute pancreatitis (RAP) who are refractory to medical or endoscopic therapy.[2,5]

Total pancreatectomy with islet autotransplantation (TPIAT) is a definitive surgical intervention for CP in which the pain-inducing

pancreas requires comprehensive resection.[6] This procedure involves the meticulous isolation of islet cells from the excised pancreas, followed by subsequent autologous transplantation (Figure 1). TPIAT has analgesic effects and good outcomes in patients with CP who presented with intractable pain. Further, the TPIAT working group has a strong consensus that autologous islet transplantation after TP alleviates intractable pain caused by CP, reduces opioid use, improves QoL, and maintains glycemic control.[7] TPIAT is a multifaceted process encompassing several sequential steps, including the identification of surgical indication, pancreatectomy, isolation and transplantation of islet cells, postoperative management, and long-term care. TPIAT was initially carried out in 1977 as an experimental procedure,[8] facing numerous challenges and technological limitations during its early stages.[9] However, since then, considerable progress has been achieved in the isolation, purification, and transplantation of islet cells, leading to improved outcomes for patients with CP.[10] TPIAT has now demonstrated its ability to enhance the QoL for CP patients with refractory pain. Nevertheless, there remain several areas within the TPIAT procedure that warrant further optimization. Addressing these challenges is of paramount importance in bolstering the overall efficacy of TPIAT and expanding its potential as a viable treatment option for a broader population of CP patients afflicted with intractable pain. The current study aimed to perform a comprehensive review of the current status of and challenges in the use of TPAIT and to discuss its future prospects.

2 | SURGICAL AND NONSURGICAL TREATMENT FOR CP AND RAP

The most troublesome symptom for patients with CP is pain. The initial approach for managing pain involves lifestyle modifications, such as

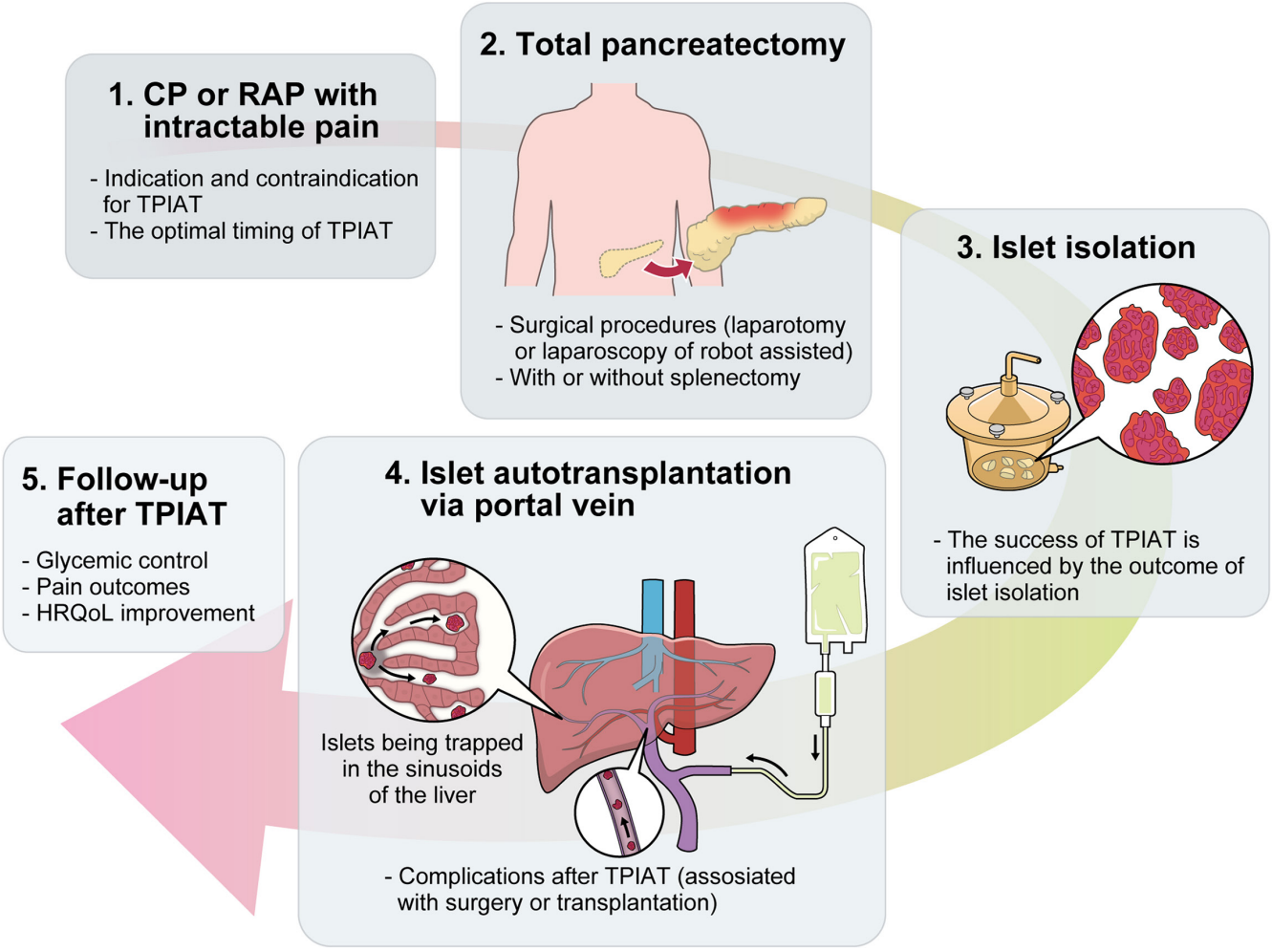

FIGURE 1 Schematic to illustrate entire process for total pancreatectomy with islet autotransplantation. (1) The common primary indication for TPIAT is chronic pancreatitis with intractable pain that is not successfully managed with medical, endoscopic, or prior surgical therapy. (2) The pancreas, which is the cause of the pain, is completely removed, but the procedures and the presence or absence of splenectomy vary depending on the facility. (3) Glycemic control is based on the number of islets isolated from the resected pancreas. (4) The isolated islets are promptly transplanted via the portal vein. (5) The long-term physical and psychological follow-up are necessary for patients who have undergone TPIAT. CP, chronic pancreatitis; HRQoL, health-related QoL; RAP, recurrent acute pancreatitis; TPIAT, total pancreatectomy with islet autotransplantation.

smoking and alcohol cessation, and the use of non-opioid analgesics including acetaminophen and NSAIDs.[11] Additionally, pregabalin is an effective adjuvant therapy for pain associated with CP.[12] Treatment with narcotics is considered in patients with refractory pain if the above-mentioned medical therapies are insufficient. However, the chronic use of opioid is independently associated with mental health disorders.[13] Celiac plexus block and celiac plexus neurolysis are a nonsurgical, nonnarcotic treatment method for controlling CP-related pain.[14] However, their pain-relieving effect is temporary, and they are associated with a risk of complications such as infection and neuropathy. Hence, appropriate patient selection must be considered.[14]

Endoscopic treatment is recommended for patients with pancreatic strictures or intraductal stones. In a randomized controlled trial comparing early surgery and endoscopic treatment, which is the initial approach for symptomatic CP, the early surgery group had lower Izbicki pain scores than the endoscopy group during an 18-month follow-up. Furthermore, the early surgery group required fewer interventions.[15] However, endoscopic treatment is initially preferred due to its less invasive nature. These findings may serve as a guide on the early selection of surgical intervention if endoscopic treatment cannot provide sufficient pain relief.

The surgical approaches may include drainage alone, pancreatectomy, and total pancreatectomy (TP), which is selected based on the patient's specific CP status.[16,17] If the main pancreatic duct is dilated, surgical procedures aim to decompress or resect the inflamed tissue.[18] Combined drainage and local resection, such as Frey procedure[19] and Beger procedure,[20] are alternative methods to major resection and have promising outcomes, particularly symptom relief and low morbidity and mortality rates.[21] Conversely, in patients with CP without ductal dilation, pancreatic resection is selected based on the location of the pancreatic lesion, with TP reversal in cases where the lesion is distributed throughout the pancreas.[5] TPIAT can facilitate insulin independence and can be superior to TP alone in terms of glycemic control and long-term diabetes outcome. Therefore, the TPIAT working group recommends IAT if there is no implementation environment or economic barriers.[7]

3 | INDICATION AND TIMING OF TPIAT

Table 1 shows the indications for TPIAT based on previous studies.[22–24] Intractable pain is the common primary indication for TPIAT in patients with impaired QoL due to CP or RAP that was not successfully managed with medical, endoscopic, or prior surgical therapy. Patients with hereditary/genetic pancreatitis are suitable candidates for TPIAT, with consideration of its efficacy in inhibiting pain and preventing recurrent pancreatitis and pancreatic cancer.[25,26] Contraindications for TPIAT vary by institution, for example, the University of Minnesota lists alcoholism, the presence of pancreatic cancer, IPMN, and uncontrolled mental illness as contraindications for TPIAT.[22] In some institutions, patients with diabetes or pre-diabetes can undergo TPIAT, which improves residual pancreatic islet and alpha cell functions,[27] if there is endogenous islet function.[28] Table 2 and Figure 2 show the demographic characteristics of studies on TPIAT for CP and RAP at institutions in the United States, United Kingdom, and Australia.[22,29–33]

The optimal timing of TPIAT is a sensitive issue. In recent years, previous studies have reported the superiority of early surgical intervention to nonsurgical treatment for CP.[15,26,34,35] However, the study cohorts commonly underwent pancreatic-sparing surgery, and these studies did not provide a reference for determining the timing of TP or TPIAT. There is no consensus on the timing of TPIAT due to lack of studies including head-to-head comparisons of TPIAT with other therapeutic options.[7] The decision to implement TPIAT, which results in the removal of one organ, should be made on a case-by-case basis by a team of specialists who can evaluate the individual patient's needs and can develop a personalized treatment plan.

4 | SURGICAL PROCEDURES

TP in TPIAT differs from TP for pancreatic cancer. Hence, surgeons should pay attention to these variations. That is, TP in TPIAT is generally performed to decrease the warm ischemic time and maximize the protection of islet cells[36] to the greatest extent. The general surgical procedure is as follows. First, the Kocher maneuver is performed to completely mobilize the duodenum and pancreatic head. Next, the greater omentum and the short gastric artery are dissected, and the pancreatic tail splenic hilum is freed from the stomach. Then, the spleen and pancreatic dorsal portion are de-rotated from the dorsal aspect of the spleen. The whole pancreas is completely mobilized. However, the blood supply to the pancreas is preserved at this point.[37,38] Currently, the second, third, and fourth portions of the duodenum are generally resected and the pylorus is preserved.[36] Nevertheless, the distal stomach and entire duodenum are resected based on the extent of peripancreatic inflammation and prior surgery.[39] Finally, the gastro-duodenal artery, splenic artery, and splenic vein are dissected in this order, and the pancreas, duodenum, and spleen are removed. At the back table, the duodenum and spleen are removed via sharp dissection and the pancreatic duct is cannulated. The pancreas is then immediately placed in a cold sterile preservative solution and transported to the islet isolation laboratory.

Coluzzi et al. reported that it is often difficult to preserve blood vessels around the spleen in patients with chronic pancreatitis because of inflammation and tissue necrosis, and splenectomy is performed in most cases of TPIAT.[40] However, they also mentioned that TPIAT with full spleen preservation and arterial/venous preservation did not affect the yield or function of islet cells ensuring the safety and effectiveness of TPIAT.[40] In recent years, laparoscopic[41–43] or robotic-assisted[44] TPIAT has been considered a minimally invasive surgery, and its safety and efficacy are similar to those of open surgery. However, these approaches are associated with prolonged warm ischemia time, and further investigation is required to optimize its safety and efficacy.

The continuity of the gastrointestinal tract is restored by Roux-en-Y duodeno-(or gastro)-jejunostomy, duodenoduodenostomy, or duodeno-(or gastro)-jejunostomy, which may vary based on the

TABLE 1 Published criteria about TPIAT for pancreatitis.

Minnesota criteria[22]
1. Documented CP or RAP with chronic or severe abdominal pain, that directly results in at least one of the following: a. Chronic narcotic dependence (narcotics required on a daily or near-daily basis for >3 months) b. Impaired quality of life (QOL), per the RAND Medical Outcomes Study 36-Item Short-Form Health Survey 2. Complete evaluation without reversible cause of CP or RAP (present or untreated) 3. Unresponsiveness to the maximal medical therapy and endoscopic therapy 4. Ongoing abdominal pain caused by CP or RAP requiring routine narcotic treatment 5. Adequate islet function (i.e., either without diabetes or non-insulin-requiring diabetes with positive C-peptide levels)
South Carolina criteria[23]
1. CP or RAP 2. Debilitating pain: defined as the daily narcotic use and/or inability to work, attend school, or engage in normal social roles 3. Not amenable to other interventions: Includes medical, endoscopic, and lesser surgical options 4. Physiologically fit: absence of prohibitive cardiopulmonary conditions and significant hepatic disease 5. Psychologically fit: Requires behavioral medicine evaluation
Milan Protocol[24]
I. Clinical indications for TPIAT (pancreatitis)
CP: in cases of nondilated duct without any cephalic mass when subtotal or total pancreatectomy is indicated (refractory pain in patients with failed medical therapy) RAP: in cases of relapsing disease (≥3 episodes over >6 months without evidence of current gallstone or other correctible etiology)
II. General indications for TPIAT (must have each of the following)
1. Age >18 years 2. Fasting blood sugar level of <126 mg/dL without glucose-lowering medications 3. Ability to provide written informed consent 4. Mental stability and ability to comply with the study procedures

Abbreviations: CP, chronic pancreatitis; RAP, recurrent acute pancreatitis; TPIAT, total pancreatectomy with islet autotransplantation.

intraperitoneal condition and institutional policy.[10,29,31] Biliary reconstruction commonly involves choledocho- or hepatico-jejunostomy, and choledochoduodenostomy is not frequently performed.[29]

5 | ISLET ISOLATION AND TRANSPLANTATION

Glycemic control and C-peptide positivity are based on the number of islets isolated from the resected pancreas.[37] The success rate of IAT can increase by improving the islet yield.[45] Therefore, islet isolation is the most important step in TPIAT. At several institutions, the modified Ricordi method is used in islet isolation procedures.[46] In brief, the islet isolation methods are as follows: The procured and cold-preserved pancreas is distended with a cold enzyme solution via the pancreatic duct with appropriate pressure and by raising the temperature to 37°C. Next, the Ricordi chamber is shaken to mechanically facilitate dispersion and free the islet.[46] Islet cells are then purified from materials that are not necessary for islet transplantation, such as exocrine materials.[47] The short-term complication rate increases with the amount of tissue transplanted; thus, in most institutions, purification is performed when the tissue volume exceeds 0.25 mL/kg after digestion.[48] However, in patients with CP, the pancreas often exhibits fibrosis or atrophy, resulting in an extremely small pellet after digestion. Therefore, such cases sometimes do not require purification.[49] At this stage, the patient is still in the operating room with general anesthesia and open laparotomy incision. Isolated islets are infused into the portal system while paying attention to an elevated portal pressure.[49] If the pressure reaches 25 cm water, the infusion is discontinued, and any remaining tissue is discarded or placed in the peritoneal cavity.[37] Table 3 shows the summary of islet isolation outcomes in TPIAT in several studies.[6,29–32,37,50]

At centers with an islet isolation facility, both pancreatectomy and islet isolation can be performed. By contrast, at centers without these facilities, remote islet isolation is conducted. The explanted pancreas is transported to another facility, and islet isolation is then performed. Next, the explanted pancreas is returned to the original center for infusion into the patient.[51] Although CIT may worsen the transplantation outcomes with this procedure, remote TPAIT does not worsen islet isolation outcomes, insulin independence rate, and glycemic control.[52,53] Therefore, if a system for transporting the pancreas is developed, remote isolation can be conducted at centers without isolation facilities to facilitate TPAIT.

6 | COMPLICATIONS OF TPIAT

The complications of TPAIT are primarily associated with surgical factors. Meanwhile, islet autotransplantation-related complications are rare.[38] Infections, including surgical site infection, pneumonia, urinary tract infection, and sepsis, are the most common complication of TPAIT.[54,55] Infectious complications are more likely to occur with a longer CP duration.[56] Delayed gastric emptying (DGE) is the second most common post-transplant complication.[38,57,58] Although DGE is not life threatening, it can be distressing to patients and health care providers due to the prolonged fasting period, and it can prolong a hospital length of stay.[57] The risk factors of DGE after pancreatectomy include postoperative pancreatic fistula and intra-abdominal infection,[59] and patients who receive TPAIT may be at risk of DGE due to a high risk of postoperative intra-abdominal infection. In addition, increased portal pressure may reduce gastrointestinal peristalsis and cause DGE.[38] The predominant approach in managing DGE typically involves conservative measures, wherein patients are subjected to fasting and administered metoclopramide and low-dose erythromycin.

Although less common than TP-related complications, the portal vein thrombosis (PVT) is commonly associated with the transplantation of islet cells[60,61] and is a potentially serious complication.[38]

TABLE 2 The demographic characteristics of the selected studies about TPIAT for CP and RAP.

Author	Year	Country	Adults or children	Number	Age (years)	Sex (M/F)	Duration of CP	Previous pancreatectomy	Preoperative diabetes	Preoperative use of narcotics
Nathan et al.[29]	2022	US	Adults	195	38.2 ± 12.9	74/121	N/A	PD, *n* = 14 (7%) DP, *n* = 11 (6%) Pancreaticojejunostomy, *n* = 8 (4%) Drainage, *n* = 5 (2.6%)	N/A	N/A
			Children	84	11.4 ± 4.1	30/54	N/A	Pancreaticojejunostomy, *n* = 2 (2%) Drainage, *n* = 1 (1.2%)	N/A	N/A
Bampton et al.[30]	2021	Australia	Both	16	Median (IQR): 22 (15–36)	5/11	N/A	N/A	N/A	Yes, *n* = 13 (81.3%) No, *n* = 2 (12.5%) N/A, *n* = 1 (6.3%)
Naples et al.[31]	2021	US	Adults	80	Median (IQR): 39 (31–50)	34/46	7 (IQR: 3–11)	DP 4, PD 1, MP(+DP) 1, Frey 2, Beger 1, Drainage 5	N/A	N/A
Morgan et al.[32]	2018	US	N/A	195	Mean: 40.3	54/141	Mean: 8.1	PD, DP, and drainage, *n* = 56 (29%)	Diabetes, *n* = 37 (19%)	N/A
Chinnakotla et al.[22]	2015	US	Adults	490	18–29, *n* = 112 (22.9%) 39–39, *n* = 140 (28.6%) 40–49, *n* = 148 (30.2%) 50–72 90, *n* = (18.4%)	123/367	7.1 ± 0.3	Puestow, *n* = 37 (7.4%) Beger or Frey, *n* = 6 (1.2%) PD, *n* = 28 (5.7%) DP, *n* = 23 (4.7%)	*n* = 38 (7.8%)	3.3 ± 0.2 years
			Children	91	3–12, *n* = 42 (46.2%) 13–17, *n* = 49 (53.8%)	41/50	5.6 ± 0.4	Puestow, *n* = 11 (12.1%) Beger or Frey, *n* = 3 (3.3%) PD, *n* = 1 (1.1%) DP, *n* = 6 (6.6%)	*n* = 3 (3.3%)	1.6 ± 0.1 years
Garcea et al.[33]	2013	UK	Adults	60	Median (range): 45 (30–69)	NA	60 (16–216)	HOP resection (8.3%) Distal resection (5.0%) Cyst drainage (5.0%)	N/A	Yes (95.0%) No (5.0%)

Abbreviations: CP, chronic pancreatitis; DP, distal pancreatectomy; HOP, head of pancreas; IQR, interquartile range; MP, middle pancreatectomy; PD, pancreatoduodenectomy; RAP, recurrent acute pancreatitis; TPIAT, total pancreatectomy with islet autotransplantation.

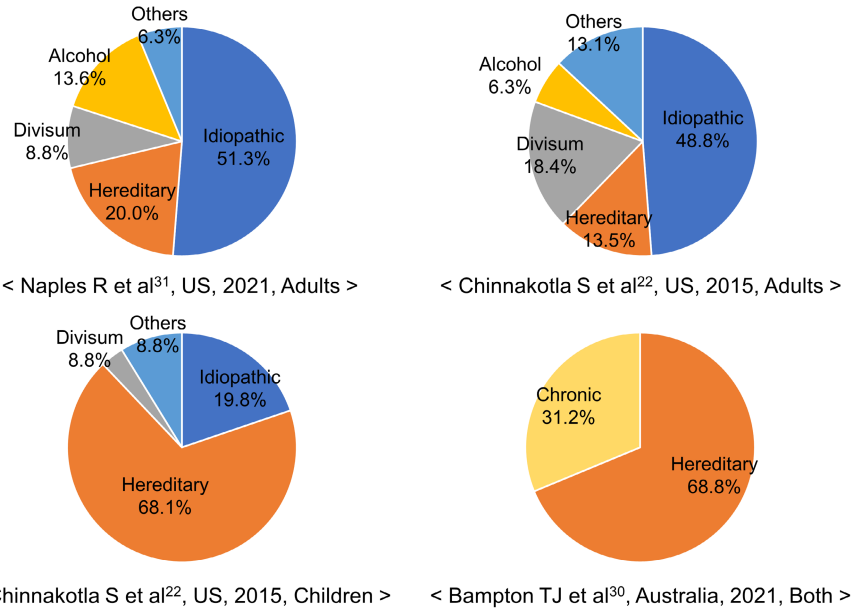

FIGURE 2 Etiologies of patients who underwent TPIAT in the selected studies. TPIAT, total pancreatectomy with islet autotransplantation.

PVT after TPAIT is correlated with transplanted islet volume and a localized inflammatory mechanism, which occurs when islet cells expressing TF are exposed to large amounts of portal blood, so-called as an instant blood-mediated inflammatory reaction (IBMIR). Nevertheless, it is independent of systemic derangements in coagulation.[60,62,63] In the context of post-TPIAT patients, the implementation of prophylactic anticoagulation (in the form of unfractionated heparin or enoxaparin administration) along with regular ultrasound screening is recommended as a means to mitigate the risk of PVT.[60]

The postoperative complications of TPAIT are significantly correlated with extended durations of hospitalization and intensive care unit stays and an increased likelihood of readmission within 30 days.[38,64] However, several reports have shown that these short-term complications do not adversely affect graft function.[38,60,64] Thus, complications must be identified at the earliest and treated appropriately.

7 | POSTOPERATIVE MANAGEMENT

Similar to islet allotransplantation, autologous islets are not completely functional immediately after transplantation, and intraoperative glycemic control with continuous intravenous insulin infusion is required against hyperglycemic toxicity.[49,65] Because the patient's own cells are transplanted, unlike the procedure used in allo-islet transplantation, no immunosuppressive drugs are administered. The subcutaneous injections of insulin are then transitioned to maintain euglycemia within the first 3 months after TPAIT. Moreover, exogenous insulin can continually reduce functional stress in beta cells during the engraftment (angiogenesis) stage.[6] The exogenous insulin dose is then tapered with a target Hba1c level of ≤6.5%, and insulin therapy is continued if this is not achieved.[6]

In a previous study, after a long-term follow-up of patients who received TPAIT at the University of Minnesota, the post-transplant insulin independence rates were 22.3% at 5 years and 20.0% at 10 years, with patients maintaining a partial graft function of 60% at 5 years and 47.1% at 10 years.[6] Moreover, in patients at the Medical University of South Carolina, the insulin withdrawal rate after TPAIT was 23% at 5 years.[32] Furthermore, the health-related QoL (HRQoL) has improved after TPAIT even in patients who are insulin-dependent.[65] Therefore, TPAIT is more effective than TP alone for CP.

There are various reports on the factors contributing to good graft function (e.g., insulin independence rate) after TPAIT. However, several studies have shown that patients who have achieved insulin independence have been transplanted with a high proportion of islets.[30,32,37,53] As mentioned in the previous text, the islet isolation step is, therefore, an extremely critical step and should be performed with a skillful technique. The other associated factors include CP duration,[66] smoking,[32] and preoperative diabetes.[28] Hence, patients with preoperative diabetes have a lower rate of insulin independence after TPAIT. However, these patients still experience benefits that include pain relief and presence of transplanted islets.[67] Therefore, the number of TPIATs administered to patients with diabetes will also increase in the future.

8 | PAIN AND HRQOL ASSESSMENT AFTER TPIAT

Pain outcomes after TPAIT are often assessed based on changes in narcotic independence rates and morphine dosage. Sutherland et al.[37] performed a large-scale cohort study showing that 94% of patients experienced pain improvement 1 year after TPAIT, and the rate of narcotic use decreased to 51% after 24 months. Morgan et al. reported that the preoperative use of oral morphine decreased from 208 mg/day to a mean of 60 mg at 1 year and 64 mg at 2 years. Further, it remained stable at a mean of 69 mg at 5 years postoperatively.[32]

TABLE 3 Outcomes of the selected studies about TPIAT for CP and RAP.

Author	Year	Country	Adults or children	Number of participants	Transplanted islets (IEQ/kg)	Complications	Insulin independence	Use of narcotics	HRQoL
Nathan et al.[29]	2022	US	Adults	195	2909 (IQR: 1555–4479)	PVT, *n* = 20 (10%) Abdominal infection, *n* = 16 (9%) Wound infection, *n* = 6 (3%) Bleeding, *n* = 6 (3%) Bile duct leak, *n* = 2 (1%) Bile duct obstruction, *n* = 2 (1%)	N/A	N/A	N/A
			Children	84	4577 (IQR: 2816–6517)	PVT, *n* = 2 (2%) Abdominal infection, *n* = 3 (4%) Wound infection, *n* = 2 (2%) Bleeding, *n* = 2 (2%) Bile duct leak, *n* = 1 (1%) Bile duct obstruction, *n* = 1 (1%)	N/A	N/A	N/A
Bampton et al.[30]	2021	Australia	Both	16	4224 (IQR: 2505–7301)	2 (12.5%) patients required laparotomy for postoperative complications 1 (6.3%) patient died due to myocardial infarction 3 days after TPIAT	8 (50%) patients achieved insulin independence after a median of 24 (14–45) months since transplantation.	Narcotic independence: 86.7%	N/A
Naples et al.[31]	2021	US	Adults	80	4049 (IQR: 2934–5365) in the <60 units/kg heparin group 5697 (IQR: 4140–6527) in the ≥60 units/kg heparin group	Infectious complications, *n* = 15 (18.8%) Postoperative hemorrhage, *n* = 7 (13%) DGE, *n* = 3 (3.8%) Small bowel obstruction, *n* = 2 (2.5%) Others, *n* = 7 (8.8%)	N/A	N/A	N/A
Bellin et al.[6]	2019	US	Both	215	Mean ± SD: 3462 ± 2261	N/A	1 year, *n* = 58 (27%) 5 years, *n* = 48 (22.3%) 10 years, *n* = 28 (20%)	Narcotic use: 1 year (54%) 10 years (36%)	The overall raw scores of the eight SF-36 subscales after surgery were significantly higher than those before surgery.

(Continues)

TABLE 3 (Continued)

Author	Year	Country	Adults or children	Number of participants	Transplanted islets (IEQ/kg)	Complications	Insulin independence	Use of narcotics	HRQoL
Morgan et al.[32]	2018	US	N/A	195	Mean: 3253	Clavien-Dindo score of ≥3, $n=37$ (19%)	1 year (29%) 2 years (28%) 5 years (23%)	Narcotic use: pre-TPIAT, 208 mg/day 1 year, 60 mg/day 2 years, 64 mg/day 5 years, 69 mg/day	The mental and physical quality of life scores of the SF-12 increased at 1, 2, and 5 years postoperatively.
Wilson GC et al.[50]	2015	US	Both	84	Mean ± SEM: 6342 ± 439	Intraabdominal abscess, $n=8$ (9.5%) Postoperative hemorrhage, $n=5$ (6.0%) Portal vein thrombosis, $n=2$ (2.4%) ARDS, $n=1$ (1.2%)	31 (36.9%) patients achieved insulin independence after a median follow-up of 17.1 (9.5–27.4) months	Narcotic independence: 49 (58.3%)	30 (88.2%) patients experienced an overall improvement in the SF-36 QoL survey scores.
Sutherland DE et al.[37]	2012	US	Both	409	<2500 IEQ/kg (36%) 2501–5000 IEQ/kg (39%) >5000 IEQ/kg (39%)	Bleeding, $n=9.4\%$ Anastomotic leaks, $n=4.2\%$ Intra-abdominal infection, $n=1.9\%$ Wound infections, $n=2.2\%$ Others, $n=4.7\%$	1 year (28%) 2 years (32%) 3 years (30%)	Narcotic independence: 1 year, 46% 2 years, 49%	The SF-36 integrated survey showed a significant improvement in each HRQOL scale measured after TPIAT.

Abbreviations: ARDS, acute respiratory distress syndrome; CP, chronic pancreatitis; DGE, delayed gastric emptying; HRQoL, health-related quality of life; IEQ, islet equivalent; IQR, interquartile range; PVT, portal vein thrombosis; RAP, recurrent acute pancreatitis; SD, standard deviation; SEM, standard error of the mean; SF, short-form; TPIAT, total pancreatectomy with islet autotransplantation.

Although there are several studies reporting that TPIAT resolves preoperative pain, some patients presented with new characteristic abdominal pain, possibly as a result of postoperative persistent gastrointestinal motility disorders and/or persistent central sensitization.[6] Moran et al.[68] reported that a prior history of RAP was the only factor associated with resolution of preoperative abdominal pain postoperatively. Hence, caution should be observed during TPIAT in patients with a history of CP but without a history of RAP.[68]

The effect of TPIAT is often evaluated comprehensively based on HRQoL outcomes. Georgiev et al. showed improvement in eight SF-36 subscale scores at 1 year. Meanwhile, there was a faster improvement in some subscales after surgery, thereby evidently showing the therapeutic effects of TPAIT on patient lives.[69] Bellin et al.[6] reported that even patients who were not completely weaned off narcotics experienced improvement in QoL based on the SF-36 score. Therefore, patients should be evaluated post-TPAIT using not only pain but also QoL, and the inability to wean off narcotics does not necessarily indicate treatment failure.

9 | TPIAT IN CHILDREN

Chronic pancreatitis in the pediatric population is relatively uncommon compared to adults, accounting for the incidence ranges from 0.5 to 1.46/100 000 person years.[70] Genetics is the most common risk factor for the development of CP or ARP. Approximately 73% of children with CP have one or more mutations in the pancreatitis-related genes (e.g., CFTR, SPINK1, PRSS1, and CTRC).[70] In this specific patient population, with the high likelihood of progressive CP, the absence of anatomic characteristics that can allow surgical drainage procedures or local resections and the life-time risk of pancreatic adenocarcinoma, timely intervention can have a profound and long-term influence on long-term prognosis in pediatric patients.[71]

The decision to introduce TPAIT in pediatric patients is more complex than that in adult patients, and it requires cautious consideration. CP that is refractory to medical therapy is the indication for TPAIT in pediatric patients with CP, which is similar to that in adults. Further, it is evaluated by a multidisciplinary team that includes pediatric subspecialists in the following areas: transplant surgery, gastroenterology, pain management, endocrinology, and psychology.[71] It exposes patients to the long-term risk of diabetes and its associated complications. Therefore, patients and parents should receive comprehensive counseling and appropriate guidance regarding the potential outcomes and complications of TPAIT.[72]

Surgical procedures in children with TPAIT differ from those in adults. The important surgical steps in pediatric patients include special techniques to prevent any inadvertent injury or spasm of the small vessels to the pancreas.[73] According to the Prospective Observational Study of TPAIT study, splenectomy is performed in 100% of children and in 93% of adults. Moreover, the pylorus of children was more commonly preserved than that of adults.[29] In terms of gastrointestinal tract reconstruction, Roux-en-Y duodenojejunostomy was performed on 92% of children to decrease the risk of postoperative gastrointestinal complications such as bile reflux gastritis.[73] Pediatric patients had a higher number of transplanted islets yields than adult ones,[22,29] which is attributed to the shorter disease duration of CP in children than in adults. The postoperative complication profiles of pediatric TPAIT were similar to those of adults. However, the incidence of PVT in children is significantly lower than that in adults.[29] In addition, bile leaks and bile obstructions were less observed compared with other complications despite the small bile duct of children.[71,74] The late-onset complications of pediatric TPIAT may include severe infections, which are known as overwhelming post-splenectomy infection (OPSI),[75] and the development of complications similar to those observed in standard surgical procedures. However, there are no detailed reports about these issues, making them important subjects for future investigation.

Pain relief and HRQoL improvement after TPIAT in pediatric patients are generally favorable. An analysis of 75 pediatric TPIAT cases at the University of Minnesota reported that pain and pain severity caused by pancreatitis significantly improved over time after TPIAT and the use of narcotics significantly decreased.[73] In addition, the HRQoL scores significantly improved after TPIAT, and the percentage of parents reporting that their children's condition prevented them from attending school gradually declined. After 2 years, the number became negligible.[73] The rate of insulin independence after TPAIT in children was significantly higher than that in adults, and the graft failure rates were significantly lower in children than in adults.[22] Bellin et al. showed that young children aged under 8 years had high insulin independent rates and good glycemic control.[74] Therefore, the mechanisms underlying the high rate of diabetes success in young children is attributed to the capacity of young beta cell expansion and growth.[74] These data can encourage the implementation of TPAIT in young children with CP who are hesitant to undergo major surgery.

10 | TPIAT IN JAPAN

To date, the implementation of TPIAT in Japan is limited.[76] In Japan, islet allo transplantation has not been widely accepted because a multicenter clinical trial of clinical islet transplantation has been conducted very recently and it was accepted for insurance coverage only in 2020 based on the positive results of the trial. Additionally, TPIAT is not well known in Japan, and although Japanese guidelines for the treatment of chronic pancreatitis strongly recommend a surgical treatment that is not amenable to endoscopic therapy, there is no mention of TPIAT in these guidelines.[5] Therefore, islet allotransplantation is expected to become widely used in Japan in the future, and awareness of TPIAT will spread concomitantly. To facilitate the future dissemination of evidence in Japan, the accumulation of a robust dataset of Japanese cases is indispensable. A case series of five Japanese patients receiving TPAIT had good graft function and improved pain scores and QoL 12 months after transplantation.[77] Hence, TPAIT, which has good outcomes among patients in Europe and the United States, is also applicable to Japanese people.

In 2016, the estimated number of CP patients in Japan was 56 520, the prevalence rate was 44.5 per 100 000, the newly diagnosed CP was 14 740, and the incidence was 11.6 per 100 000.[78] These numbers are roughly similar to those of Western countries.[79] In 2009, the Japanese clinical diagnostic criteria for CP were proposed, which was unique in that the world's first diagnostic criteria for early CP were proposed.[80] In 2019, the Japan Pancreas Society proposed the new Japanese diagnostic criteria, which newly incorporated pancreatitis-associated genetic abnormalities into the diagnostic criteria for CP.[81] Therefore, it may be possible to diagnose cases of chronic pancreatitis that are expected to undergo an intractable course at an early stage, and TPIAT may be an effective treatment option for such cases.

However, there are several difficulties in the implementation of TPIAT in Japan. First, although there are many facilities in Japan that perform islet isolation, only a few have experience with TPIAT. Additionally, because of the shortage of donors, only a few facilities can consistently perform islet isolation. Sharing of experience among facilities is desirable. A multicenter clinical trial (jRCTc030220161, with five participating centers) is currently being conducted to verify whether TPIAT can be a therapeutic option in Japan.

11 | CONCLUSION

TPAIT can significantly promote pain relief and improve HRQoL. Therefore, it can be a promising treatment option for patients with CP-related intractable pain. Further improvement in TPAIT is expected in the near future due to the development of less invasive surgical and pancreatic islet isolation techniques. In Japan, the initiation of clinical trials has shown growing interest and the potential for the progress and adoption of this therapeutic approach. The application of TPAIT in Japan and other countries is favorable with the expansion of its availability and the optimization of patient outcomes.

AUTHOR CONTRIBUTIONS

KY wrote the manuscript and tables. TA, KN, TI, and EH supervised the whole editing process.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest for this article.

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