Pain Control, Glucose Control, and Quality of Life in Patients With Chronic Pancreatitis After Total Pancreatectomy With Islet Autotransplantation: A Preliminary Report

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ABSTRACT

Background. Total pancreatectomy (TP) is offered as a last treatment option for pain relief in patients with chronic pancreatitis. Concurrent islets autotransplantation (TP-IAT) may improve glucose control.

Methods. We analyzed results in 20 recent patients who underwent TP-IAT at The University of Chicago. The median observation period was 28 months (2–38). Data were collected prospectively then analyzed retrospectively.

Results. The number of patients requiring opioids daily for pain control decreased from 16 (80%) prior to surgery to 2 (13%) 1 year after, with only 1 (6.5%) patient experiencing persistent phantom pancreatic pain. Opioid requirements decreased from a median 56.3 (0–240) morphine equivalent dose to 5 (0–130) on day 75 and to 0 (0–30) at 1-year follow up. Five patients (25%) completely stopped insulin support prior to day 75 while maintaining hemoglobin A1c of 5.9% (5–6.3). Eight (53%) patients were insulin free at 1 year with A1c of 6% (5.5–6.8) and a similar rate persisted in next 2 years. For the remaining patients, the more islet function that was preserved, the less insulin they required and A1c was closer to optimal. Quality of Life (QoL) measured by SF36 Physical (PCS) and Mental (MCS) Component Score improved on day 75 ($P < .001$) and maintained improvement later on. Both PCS and MCS improved regardless of whether patient requires insulin support or not.

Conclusions. Improvements of QoL with pain resolution and good glucose control can be achieved after TP-IAT in properly selected patients with CP and intractable pain, regardless of patient insulin support status.

CHRONIC pancreatitis (CP) is an inflammatory disease leading to irreversible destruction of the pancreas initially impacting exocrine function and eventually leading to endocrine deficiency. Progression of the disease may be inevitable in some patients, especially when associated with genetic mutations (most commonly CFTR, PRSS1, and SPINK1) or other unidentified genetic factors in hereditary forms of the disease. Such defects are thought to predispose to inappropriate activation of pancreatic enzymes diffusely in the pancreatic parenchyma throughout the gland, leading to chronic inflammation and fibrosis with or without overt obstruction of the main pancreatic duct or calcific stone

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formation. The most prominent symptom of CP is recurrent or persistent epigastric pain, which is present in up to 90% of patients and often is intractable to pharmacologic intervention [1]. Constant pain was shown to be the strongest predictor of poor quality of life (QoL) and disability among all complications of CP [1]. Treatment options include pain control with narcotic administration, low fat diet, pancreatic enzyme supplements, endoscopic and surgical pancreatic duct drainage procedures, and nerve blocks. In the setting of "large-duct" disease, in which the main pancreatic duct becomes dilated due to downstream stricture formation and intraductal stone burden, drainage procedures such as lateral pancreaticojejunostomy may achieve at least temporary pain relief in about 80%. Limited pancreatic resection (eg, pancreaticoduodenectomy) may be offered to patients who demonstrate focal inflammatory disease. In other situations, the role of surgical therapy is more controversial. Patients without a dilated main pancreatic duct or dominant focus of inflammation do not have an obvious surgical target for drainage or resection. Others may have failed prior surgical or endoscopic intervention or have hereditary or genetic factors that predispose to more diffuse organ involvement, an aggressive clinical course, or an increased risk of malignant degeneration. Total pancreatectomy (TP) may be offered but has traditionally been viewed as an option of last resort because of the potential for difficult-to-control insulin-dependent diabetes. The first reports in 1977 of islet autotransplantation suggested it was possible to maintain islet cell function and decrease postoperative insulin requirements after TP [2]. In subsequent reports from an increasing number of experienced centers, particularly over the past 15 to 20 years, TP with islet autotransplantation (TP-IAT) has become an accepted option for appropriately selected patients with intractable pain, allowing not only improved glucose control but also restoration of QoL [3–6]. The aim of this study was to assess pain, glucose control, and QoL outcomes following TP-IAT in a recent group of patients who underwent this procedure at the University of Chicago Medicine.

MATERIALS AND METHODS

Study Design

To assess the results of TP-IAT, we collected prospective data including surgical technique details, amount of islet mass infused, postoperative complications, insulin use, glycemic control, opioid use, and QoL. We then analyzed these data retrospectively. Data were assessed at different time points including baseline prior to surgery, day 75, and 1 and 2 years after TP-IAT. The study was approved by the University of Chicago Institutional Review Board and conducted in accordance with the principles endorsed by the Declaration of Helsinki. All participants provided written informed consent.

Patient Selection

The diagnosis of CP was based on a clinical course of recurrent or persistent abdominal pain consistent with chronic pancreatic inflammation as evidenced by clinical history, laboratory tests, imaging, and endoscopy. A multidisciplinary team assessed and selected patients for TP-IAT based on the refractory nature of the pancreatic pain and the lack of appropriate alternative medical, endoscopic, or other surgical options. Those with active alcohol addiction or without sufficient support to follow the complex postoperative regimen were excluded from consideration for this surgical intervention.

Surgical Technique

Open TP was performed with excision of the duodenum. The spleen was spared if possible, using the Warshaw technique. To minimize ischemia to the islet tissue, splenic and gastroduodenal arteries as well as the splenic vein were preserved until final excision [3,4]. Continuity of the gastrointestinal tract was re-established by hepaticojejunostomy and gastrojejunostomy. Patients remained intubated in the operating room until islets were ready for infusion. The portal vein was cannulated under direct vision through the open abdominal wound. Islets were infused under gravity, suspended in the transplant solution containing 5% albumin and 70 U heparin per kilogram of patient body weight. Portal pressure was monitored during the infusion. Subsequently, the abdomen was closed, and the patient was extubated and taken to the intensive care unit. All patients were treated by continuous insulin infusion for at the least the first 48 hours postoperatively, and then transitioned to long-acting and sliding scale insulin.

Islet Isolation

The excised pancreas was immediately preserved with cold preservation solution SPS1 (Organ Recovery System, Chicago, Ill, United States) via the splenic artery and cannulated via pancreatic duct prior to transport to the University of Chicago Good Manufacturing Practice facility for further processing. Islets were isolated using the Ricordi method with a standard semiautomated procedure. Islet purification was performed only if necessary for high tissue volume of over 20 mL.

Pain Assessment

After surgery, patients were encouraged to wean off opioids and transition to alternative medications under the guidance of pain management specialists. Level of pain was assessed prior to the procedure, on day 75, and at 1-year follow-up visit based on opioid dose requirements standardized as morphine equivalent dose (MED) calculated with an online tool [7]. We recorded the need for periodic vs daily opioid use as well as type and location of the discomfort. Pain with the same characteristics and location as prior to the surgery was defined as phantom pancreatic pain. Discomfort with new characteristics and location was recorded as "wound or hernia related" for superficial abdominal location or "other" when related to other medical problems.

QoL Assessment

Patients' QoL was assessed using the Short Form (SF)-36 Health Survey [8]. This is comprised of 36 questions that measure 8 domains (physical role, emotional role, physical function, social function, mental health, vitality, bodily pain, and general health). It can be abridged into the physical component summary (PCS) and mental component summary (MCS) scores. We choose to apply only PCS and MCS analysis for the purpose of this preliminary report.

Table 1. Baseline Characteristics of the 20 Patients Undergoing TP-IAT

	n	%
Etiology		
Genetic mutation (SPINK1, PRSS1, CFTR)	8	40
Other hereditary	5	25
Pancreas divisum	3	15
Autoimmune	1	5
Other	3	15
Sex (M/F)	7/13	35/65
	Median	Range
Age at diagnosis, y	23	17–38
Age at TP-IAT, y	41	15–60
BMI at TP-IAT, kg/m^2	26.4	22.3–30.8
Duration of diagnosed pancreatitis, y	8.5	1–16
Number of prior ERCP-stent and/or pancreatic surgery	5	3–8
Number of acute pancreatitis episodes during previous year	5	3–7
Islet mass transplanted		
Total islet equivalent (IEQ)	228,500	72,500–379,000
IEQ/kg body weight	2980	681–5229

Abbreviations: BMI, body mass index; CFTR, cystic fibrosis transmembrane conductance regulator; ERCP, endoscopic retrograde cholangiopancreatography; IEQ, islet equivalents; PRSS1, protease serine 1; SPINK1, serine protease inhibitor Kazal type 1; TP-IAT, total pancreatectomy with islet autotransplant.

Glycemic Control

Glycemic control was assessed prior to TP-IAT, at day 75, and at 1- and 2-year follow-up visits. Patient blood glucose and insulin diary were reviewed and serum A1c was collected.

Statistical Analysis

Descriptive statistics are expressed as mean ± standard deviation or median with interquartile range (IQR) as appropriate. Data was tested for normality. The Spearman rank order correlation coefficient was used to explore the relationship between indices. To assess the significance of changes of the repeated measures we used Wilcoxon signed-rank test (2 measurements) or Friedman analysis of variance with a post hoc test (3 or more measurements). A P value of less than .05 was considered statistically significant. The statistical analyses were performed using the Statistica 12.0 (StatSoft, Poland).

RESULTS

Demographics

The analysis involves 20 of the most recent patients to undergo TP-IAT at the University of Chicago Medicine. Median age of the patients was 41 (range 15–60). There were 13 (65%) women and 7 (35%) men including 3 teenagers (ages 15, 16, and 17).

The median observation period was 28 months (range 2–38 months). All 20 patients completed day 75 follow-up visit, 15 patients completed 1-year follow-up, and 9 of them completed 2-year follow-up. Prior to surgery, 11 (55%) patients required pancreatic enzyme supplementation; despite that 6 (20%) of them complained of occasional steatorrhea and 2 (10%) needed insulin support.

Eight (40%) patients had recognized genetic mutations or variations in CFTR, PRSS1, or SPINK1. Patients had chronic pancreatitis diagnosed an average of 8.5 years prior to TP-IAT (range 1–16 years). The detailed baseline characteristics of the study group including previous treatments are presented in Table 1.

Surgical Procedure and Postoperative Complications

Median duration of the surgical procedure including waiting time for islet processing and intraoperative infusion was 9.5 hours (range 8.0–11.5). Median islet mass infused was 228,500 islet equivalents (IEQ) (range 72,500–379,000), and 2980 islet equivalents per patient's body weight in kilograms (IEQ/kg) (range 681–5229 IEQ/kg). Eight (40%) patients experienced short- or long-term postoperative complications, including fungemia (n = 1), gastrointestinal bleeding (n = 1), incisional hernia (n = 4), bowel fistula (n = 1), and wound infection (n = 3). Additionally, 2 patients developed portal vein thrombosis related to intraportal islet infusion. Partial vein thrombosis resolved completely after anticoagulation in 1 patient. Total vein thrombosis in another patient required thrombectomy with thrombolysis and transjugular intrahepatic portosystemic shunt. Periodic steatorrhea requiring adjustment of enzyme supplementation and was observed in 5 (25%) patients postoperatively. No mortality was observed.

Pain

Decreasing opioid consumption reflected alleviation of pain after the procedure. Prior to TP-IAT, 17 patients (85%) required opioids for pain control, including 16 (80%) daily and 1 (5%) periodically (Fig 1A). On day 75, only 3 (15%) individuals still required opioids daily but only one of them due to phantom pancreatic pain (Fig 1B). At the same point, the other 5 (25%) patients used opioids only occasionally (Fig 1A). At 1-year follow-up, phantom pancreatic pain persisted in the same patient. The remaining 3 individuals complained of a new type of pain related to abdominal hernia or other comorbidities (Fig 1B). Prior to the surgery, our patient population required opioids in a median dose of 56.3 MED (IQR 24.2–139.5) (Fig 1C). On day 75, MED was significantly decreased to 5 (IQR 0–23) and further to 0 (IQR 0–10) at 1-year follow-up (Fig 1C). The decrease in opioid consumption became statistically significant during the first follow-up visit on day 75 and persisted throughout the whole study period ($P < .001$).

Blood Glucose Control

The main goal of islet transplantation after TP is to provide patients with their own beta-cell mass, allowing easier blood glucose management with lower insulin requirements. In the long term, this may decrease the chance for a brittle form of diabetes with uncontrolled hypo- and hyperglycemia. Two (10%) of our patients required insulin support prior to the procedure, indicating end-stage destruction of the pancreatic

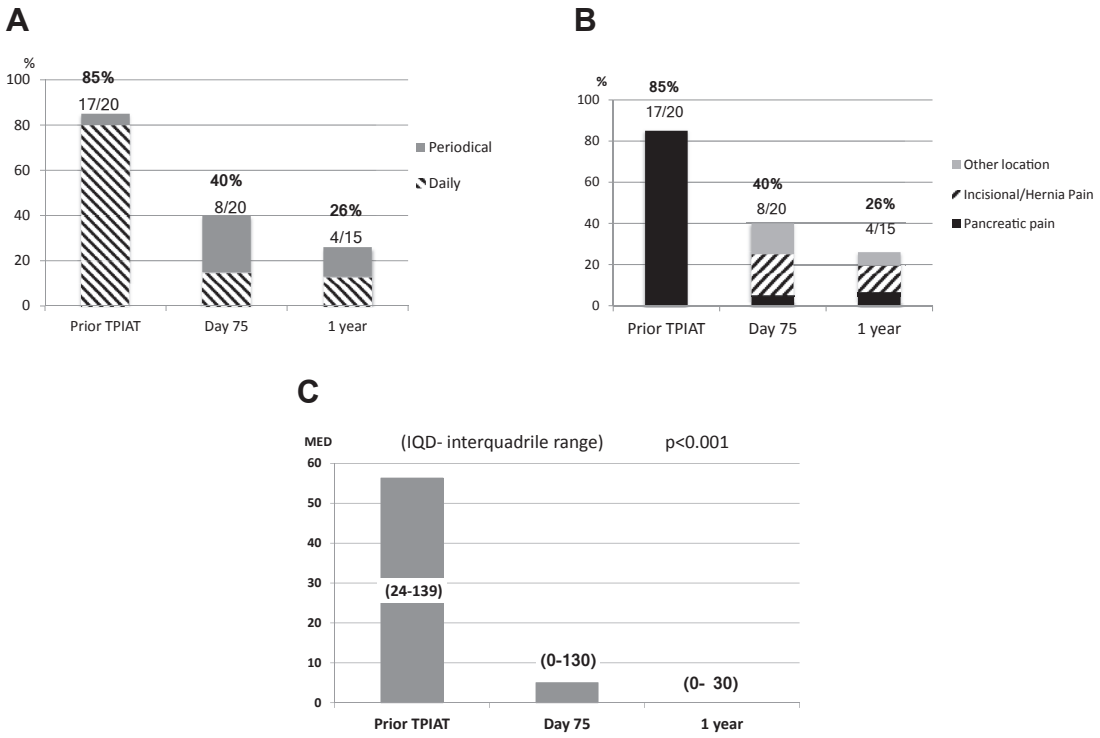

Fig 1. Pain control. **(A)** Daily versus periodical opioid use. Prior to TP-IAT, 17 (85%) patients required opioids for pain control, including 16 (80%) daily and 1 (5%) periodically. **(B)** Location of pain treated with opioids. Prior to surgery, patients required opioids due to pain related to chronic pancreatitis. On day 75 and at 1-year follow-up, only 1 (5%) patient reported phantom pancreatic pain, whereas other patients required opioids due other type of pain. **(C)** Opioid dose expressed by MED recorded in the study population (n = 20). Figure depicts significant drop of MED from 56.3 (IQR 24–139) prior to surgery to 5 (IQR 0–23) on day 75 and further to 0 (IQR 0–10) at 1-year follow-up. The decrease in opioid consumption became statistically significant during the first follow-up visit on day 75 and persisted throughout the whole study period ($P < .001$). IQR, interquartile range; MED, morphine equivalent dose; TPIAT, total pancreatectomy with islet autotransplantation.

gland, including decline in not only exocrine but also endocrine function. As expected in such situation, we were able to retrieve a very low number of islets and provided less benefit to the patients. After supporting the islet engraftment with insulin for several weeks, 5 patients (25%) stopped insulin support completely and maintained proper glucose control at day 75 follow-up with median A1c of 5.9% (range 5–6.3). Prior to 1-year follow-up, 4 additional patients stopped insulin, allowing 8 of 15 (53%) patients to be insulin independent with a maintained A1c around 6% (5.5–6.8). The percentage of patients off insulin remained around 50% during 2- and 3-year follow-ups with median A1c 5.8% (5.5–6.2) and 6% (5.4–6.6), respectively (Fig 2A). For the remaining patients, the more islet function they have preserved, the less insulin they required and glucose control has been less challenging with optimal A1c as depicted in Fig 2B. None of the patients presented signs of hypoglycemic unawareness or severe hypoglycemic episodes. Those patients who required insulin support reported occasional and mild symptomatic hypoglycemic episodes usually attributed to miscalculation of carbohydrates in their meals and overdosing insulin. Postprandial mild symptomatic hypoglycemia was noticed by a few insulin-independent patients but it resolved after adjusting diet—avoiding meals loaded with large amounts of simple carbohydrates, replacing these with more protein-dense foods, and refraining from strenuous exercise soon after meals.

Quality of Life

QoL measured based on SF-36 questionnaire improved after the TP-IAT as depicted in Fig 3A. Both PCS and MCS improved statistically on day 75 compared with prior to the surgery. Further improvements in PCS and MCS at 1- and 2-year follow-up were not significant compared with day 75.

Interestingly, improvement in QoL after TP-AIT was statistically significant regardless of whether patients require insulin support or not ($P < .05$). SF-36 PCS improved from median of 32.8 prior to surgery to 51.2 by 1 year later in patients off insulin (n = 7) and from 28.4 to 49.9 in the same time frame in the insulin-dependent group (n = 8) (Fig 3B). Similarly, SF-36 MCS improved from 39.6 to 61.6 in the insulin-free group and from 34.9 to 41.9 in insulin-dependent group as well (Fig 3C). The changes in QoL for insulin-free and insulin-dependent patients did not differ statistically.

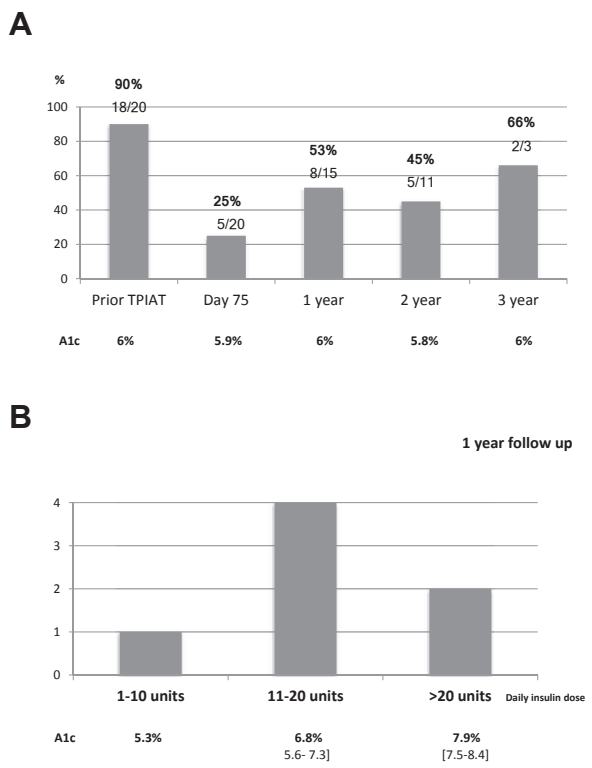

Fig 2. Glycemic control after total pancreatectomy with islet autotransplantation (TPIAT). **(A)** Insulin independence rate and A1c in study patients before and after the TPIAT. **(B)** Number of patients requiring supplementation of different dose of insulin at 1-year follow-up after TPIAT and corresponding values of A1c. The higher insulin requirements, the higher median A1c was observed. Values in brackets represent minimum and maximum value.

DISCUSSION

Severe, recurrent, or persistent abdominal pain in patients with CP remains a main debilitating factor leading to poor appetite, weakness, low energy level, anxiety, and depression that severely compromise patients' QoL. When pain becomes intractable, despite the best medical management, surgical intervention may be indicated. Although TP has traditionally been considered as a last resort [9,10], this option has become more attractive for patients in earlier stages of their disease as the techniques of islet isolation, preservation, and autotransplantation have improved. The main advantage of TP-IAT over TP alone is preservation of beta-cell mass, allowing for improved glucose control, even prevention of diabetes and enhancement in overall QoL in both the short and long term. Here, we presented the most recent results after TP-IAT in our institution.

Most of our patients obtained complete or near-complete pain relief after the procedure. Opioid use in our patients decreased over time and that trend was sustained over the whole year. Not only did fewer patients require opioids after recovery from surgery than before, but they also used them on a less regular basis, periodically rather than daily. It should also be highlighted that in the majority of patients after surgery, opioids were used to alleviate a different, new type of pain related to other medical problems such as hernia, fibromyalgia, or arthritis. Therefore, opioid usage as a measurement of outcome of TP-IAT is not optimal, possibly being confounded by different comorbidities, but remains a practical tool.

Other studies confirmed our findings. TP-IAT provided statistically significant reduction in median daily morphine requirements, and number of patients requiring regular opiate analgesia preoperatively and postoperatively [5,11]. Garcea et al reported that 97% of all patients were satisfied with their operation, with more than 90% reporting that their pancreas pain was gone completely [11]. Additionally, a recent study revealed that 55% of patients with pain due to chronic nonalcoholic pancreatitis were diagnosed with clinical depression, and 39% were at risk for opioid misuse. The authors of this study identified several factors associated with higher opioid misuse measure scores, including increased depressive symptoms, increased pain rating at the time of the office visit, and impairment of psychological QoL [12].

One of our patients presented postoperatively with phantom pancreatic pain but with decreased opioid usage from daily prior to surgery to periodically after. In another individual with an 8-year history of CP, pancreatic type of pain subsided for 6 months but reappeared. Both patients had a history of multiple endoscopic decompressions of the main pancreatic duct with stent placements. Chinnakotla et al in their analysis of over 500 cases found that patients with a prolonged duration of narcotic use (>5 years) and repetitive endoscopic stenting (>3 previous stents) before TP-IAT were more likely to have persistent pain or prolonged narcotic use postoperatively [6]. The results from multiple centers suggest that surgical intervention earlier in the course of the disease is associated with favorable outcomes (ie, improved pain control and the potential for less narcotic dependence) [13–15]. A possible explanation for this finding is the visceral and central nerve sensitization as major mechanisms underlying pain in CP, which occur over time and once developed are often refractory to definitive treatment even with radical surgery [16].

As far as blood glucose control, insulin-independence rates after TP-IAT in our patients of 25% at day 75 and around 50% afterward are consistent with reports of 24% to 40% from other institutions [5]. Our remaining patients, despite requiring postoperative insulin support, also clearly benefitted from islet autotransplantation. The more islet function patients have preserved, the less insulin they required, and it was much easier to achieve proper glucose control and maintain optimal A1c, which has important clinical implications allowing for better prevention of development of secondary diabetic complications in the long term. The critical role of function of even some islet mass measured as positive serum c-peptide has been extensively described for islet allotransplantation [17].

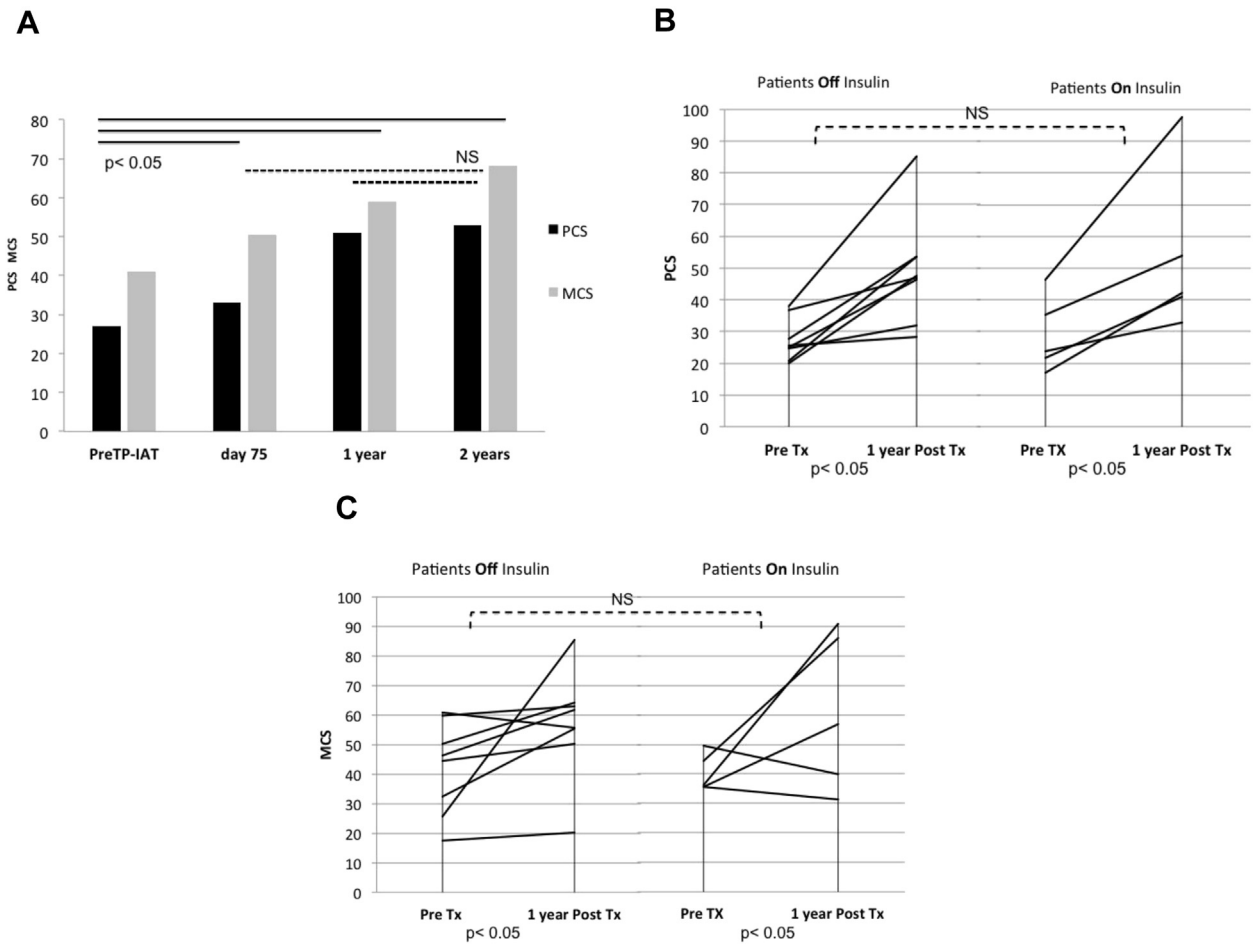

Fig 3. Improvement in QoL based on SF36 Physical Component Score (PCS) and Mental Component Score (MCS). **(A)** Both PCS and MCS improved statistically on day 75, 1year and 2 year follow up after total pancreatectomy with islet autotransplantation (TPIAT) ($P <$ .05) compared with prior to the surgery. Further improvements in PCS and MCS were not significant comparing to day 75. **(B)** Improvement in quality of life (QoL) after TPAIT based of Short Form (SF)-36 PCS was statistically significant 1 year after the procedure regardless of whether patients require insulin support or not ($P <$ .05). The changes in QoL for insulin-free and insulin-dependent patients did not differ statistically (NS). **(C)** Improvement in QoL after TPAIT based off SF-36 MCS was statistically significant 1 year after the procedure regardless of whether patients require insulin support or not ($P <$ .05). The changes in QoL for insulin-free and insulin-dependent patients did not differ statistically (NS). Tx, transplantation.

Patients with positive c-peptide have improved glucose control and lower chances for severe hypoglycemic episodes compared with those without any islet mass [17]. A study from the United Kingdom highlighted that results of islet autotransplantation were not uniform across the world. Success depends on center experience, patient population, and timing of the operation in relation to progression of the disease [11]. Insulin-independence rate after TP-IAT presented in that study was only 5% with no benefit of improvement in A1c in contrast to US centers. Such outcomes lead to delays in completing TP, because it would inevitably render patient diabetic. Subsequently, pancreas and islet destruction progress over the time, leading to even worse endocrine as well as pain control outcomes. In such situations, disappointed payers or insurance as well as patients lose enthusiasm for the procedure. The only way to brake such a vicious cycle is to identify proper candidates early for the TP procedure according to the strategy we described in the introduction, and offer them TP-IAT soon enough to preserve islet function and prevent opioid dependence.

Postprandial hypoglycemia has been described in pancreas and islet transplant patients and is most likely related to delayed inhibition of insulin secretion stimulated by a meal due to nonphysiologic location and blood supply of the islets in the patient after the transplant.

Overall, patients' QoL improved after TP-IAT in our series, which is in agreement with previous reports [6,11,13]. Improvement in QoL correlated with pain relief after the procedure allowing a return to daily activities and social and

professional life. Interestingly, QoL improved irrespective of the need for insulin supplementation after the procedure. It highlights that efforts related to maintain appropriate blood glucose control with insulin injections were not substantially compromising our CP patient QoL. Whether it would also be true for patients who undergo TP without islet autotransplantation remains to be proven. However, it is reasonable to assume that maintaining proper glucose control is much more challenging for patients without any islets—without not only any beta-cell mass but also alpha cells than for type 1 diabetic patients who lack only beta cells and struggle with glucose control already. In contrast, islet autotransplantation allows patients to restore some of their own islet mass so even if patients need some insulin support, they more resemble type 2 diabetic individuals with much easier glucose control. Nevertheless, how much hardship of glucose control would affect improvement in QoL in patients after TP in comparison with TPIAT still remains to be assessed. Independently, it was shown that CP has more detrimental effect on patients' QoL than diabetes, which highlights the value of CP relief procedures even at the cost of diabetes [18].

Our patients' QoL improved despite experiencing various surgery-related complications. Our 40% rate of adverse events is similar to the rate presented by Morgan et al [19], and the 10% incidence of portal vein thrombosis is slightly higher when compared with the 0% to 4.2% rate reported by others [20,21]. Therefore, we have modified our clinical protocol recently, limiting use of spinal anesthesia, which requires a lower dose of heparin in postoperative thromboembolic prophylaxis. We had no perioperative or late mortality, which was an important factor to achieve presented outcomes.

Limitations of the study include that it is a single-center analysis with a low number of patients and related to application of TP-IAT only in highly selected patients. Being aware of the above shortcomings and to increase the potential of the study, authors are currently collaborating in a multicenter trial to validate these findings.

In conclusion, TP-IAT improved QoL in properly selected patients with CP and intractable pain, with resolution of chronic pain and favorable glucose control regardless of procedure-related complications and the need for insulin supplementation.

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