ORIGINAL ARTICLE

Morbidity of total pancreatectomy with islet cell auto-transplantation compared to total pancreatectomy alone

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Abstract

Background: In pancreatitis, total pancreatectomy (TP) is an effective treatment for refractory pain. Islet cell auto-transplantation (IAT) may mitigate resulting endocrinopathy. Short-term morbidity data for TP + IAT and comparisons with TP are limited.

Methods: This study, using 2005–2011 National Surgical Quality Improvement Program data, examined patients with pancreatitis or benign neoplasms. Morbidity after TP alone was compared with that after TP + IAT.

Results: In 126 patients (40%) undergoing TP and 191 (60%) patients undergoing TP + IAT, the most common diagnosis was chronic pancreatitis. Benign neoplasms were present in 46 (14%) patients, six of whom underwent TP + IAT. Patients in the TP + IAT group were younger and had fewer comorbidities than those in the TP group. Despite this, major morbidity was more frequent after TP + IAT than after TP [n = 79 (41%) versus n = 36 (29%); P = 0.020]. Transfusions were more common after TP + IAT [n = 39 (20%) versus n = 9 (7%); P = 0.001], as was longer hospitalization (13 days versus 9 days; $P < 0.0001$). There was no difference in mortality.

Conclusions: This study is the only comparative, multicentre study of TP and TP + IAT. The TP + IAT group experienced higher rates of major morbidity and transfusion, and longer hospitalizations. Better data on the longterm benefits of TP + IAT are needed. In the interim, this study should inform physicians and patients regarding the perioperative risks of TP + IAT.

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Introduction

In pancreatitis, total pancreatectomy (TP) is an effective treatment for refractory pain; however, the resulting loss of pancreatic islet cells results in brittle diabetes with potentially volatile blood sugars. Islet cell auto-transplantation (IAT) is an attempt to mitigate this serious and permanent endocrinopathy resulting from TP. Whereas pancreatitis is seen and treated worldwide, TP + IAT is limited to relatively few centres. Physicians and surgeons who treat refractory pancreatitis must debate whether patients should be preferentially referred to centres for TP + IAT over TP alone. Given the infrequency of TP and TP + IAT, data on the short-term morbidity associated with either procedure are limited.

The benefits of TP, with or without IAT, include reductions in chronic pain and narcotic use, and better function. Garcea *et al.*[1] found the proportion of patients using opiates decreased from 90.2% preoperatively to 15.9% at 5 years. However, TP + IAT is an imperfect solution to post-TP endocrinopathy because many

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ACS-NSQIP Disclaimer

The American College of Surgeons National Surgical Quality Improvement Program and the hospitals participating in the ACS NSQIP represent the source of the data used herein; these institutions have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

patients require insulin in the long term. In a recent meta-analysis of outcomes after TP + IAT, insulin independence was found to amount to 27% at 1 year and 21% at 2 years.[2]

Because TP + IAT is surgically quite different from TP, the associated risks and morbidity are unique. A retrospective study of 26 patients demonstrated a morbidity rate of 56% with TP + IAT.[3] Another series showed that re-laparotomy was required in 15.9% of patients and that bleeding was the most common complication.[4] By contrast, series of TP alone have shown morbidity rates of 36.5–39.0%, and a reoperation rate of 5%.[5,6] Despite its potential benefits, the risks associated with TP + IAT appear to be greater than those associated with TP alone.

This study employed a nationwide, prospective, clinical database to compare perioperative outcomes in patients undergoing TP alone with those in patients submitted to TP + IAT. This may serve to better inform physicians and counsel patients regarding the risks of referral for TP + IAT.

Materials and methods

Data source and inclusion criteria

This was an observational study using National Surgical Quality Improvement Program (NSQIP) data for 2005–2011. The NSQIP database is a surgical outcomes research effort organized by the American College of Surgeons (ACS). For selected patients, a specially trained nurse reviewer collects data on preoperative comorbidities, intraoperative parameters, and 30-day postoperative morbidity and mortality. The database is de-identified and therefore this study was exempt from the institutional review board process.

This study examined the primary and all concurrent procedure fields for current procedural terminology (CPT) codes for eligible patients. The TP group included any patient with the CPT code 48155, in the absence of any code for IAT. The TP + IAT group included any patient with the CPT code of 48160. In addition, patients were included in the TP + IAT group if they had the CPT code 48155 (total pancreatectomy) and a separate IAT code of 0141T, 0142T, 0143T, G0341, G0342, G0343 or S2102. Only patients submitted to concurrent IAT, performed in the operating room, were considered in this analysis. Patients in whom surgery was deemed emergent or in whom disseminated cancer was found were excluded. Patients who carried a postoperative diagnosis of pancreatitis or benign neoplasm (codes 577*, 211*, 157* or 171*) were selected. The final population comprised all patients who underwent elective TP and might have been candidates for IAT.

Data and outcomes

The study examined standard demographic data, postoperative diagnosis, and the following comorbidities as potential predictors of outcome: (i) diabetes; (ii) cardiac disease (hypertension, angina, previous myocardial infarction, cardiac angioplasty or bypass surgery); (iii) active pulmonary disease (pneumonia and severe chronic obstructive pulmonary disease), and (iv) nutritional status (weight loss and albumin).

The primary outcome was major morbidity. Major morbidity was defined as re-intubation, prolonged intubation, pneumonia, cardiac arrest, myocardial infarction, renal failure requiring dialysis, deep or organ space infection, pulmonary embolus, transfusion requirement, sepsis, shock, stroke or coma.[7] Minor morbidity was defined as urinary tract or superficial wound infection, deep vein thrombosis, or creatinine elevated by >2 mg/dl above baseline without the need for dialysis. The other outcomes examined were mortality, and cardiac, pulmonary, wound-related, infectious, hemorrhagic and venous thromboembolic (VTE) morbidity.

Statistical analysis

Mean and median values were used to describe continuous data. Discrete variables were displayed as frequencies. For bivariable analyses, two-tailed *t*-tests and Mann–Whitney *U*-tests were used to compare continuous data as appropriate according to the distribution of the data; Fisher's exact or chi-squared tests were used for categorical variables. Multivariable regression analysis was employed to attempt to adjust for confounders. Separate multivariable models for regression analyses of major and minor morbidity were derived. *A priori*, age and American Society of Anesthesiologists (ASA) class of ≥3 were included as covariables as a result of their known associations with morbidity and mortality. Additional eligible covariables were those that: (i) differed between groups at baseline, and (ii) showed association with the outcome on univariate analysis. To ensure the most parsimonious model, eligible covariables were run through a stepwise selection process and only covariables with a *P*-value of <0.1 were included in the final models. The Hosmer–Lemeshow test was used to check goodness of fit. A predetermined subgroup analysis of only patients with pancreatitis, excluding patients with a diagnosis of benign neoplasm (code of 211*), was conducted. All statistical analysis was performed using STATA SE Version 12 (StataCorp LP, College Station, TX, USA).

Results

Population characteristics

Of 607 patients undergoing eligible TPs, 14 (2%) emergency patients and 24 (4%) patients with disseminated cancer were excluded. Patients with a postoperative diagnosis of malignancy ($n = 186$), carcinoma *in situ* ($n = 10$) or an unknown diagnosis ($n = 56$) were excluded. The final study sample consisted of 317 patients, of whom 126 (40%) underwent TP alone and 191 (60%) underwent TP + IAT. The most common postoperative diagnosis was chronic pancreatitis ($n = 244$, 77%). The majority of patients with benign neoplasms underwent TP and only six of 46 (13%) patients underwent TP + IAT ($P < 0.001$). The most common comorbidities were diabetes ($n = 60$, 19%) and hypertension ($n = 84$, 26%).

Patients undergoing TP + IAT were generally healthier (Table 1). They were younger and had less commonly experienced

Table 1 Characteristics of the study population ($n = 317$)

	TP group $n = 126$ (40%)	TP + IAT group $n = 191$ (60%)	*P*-value
Age, years, median (range)	54 (18–78)	40 (18–70)	< 0.0001
Male, *n* (%)	51 (40%)	48 (25%)	0.006
Active tobacco use, *n* (%)	42 (33%)	60 (31%)	0.720
Alcohol abuse, *n* (%)	3 (2%)	0	0.059
Weight loss of > 10% in 6 months, *n* (%)	15 (12%)	11 (6%)	0.051
Albumin, g/dl, median (range)	3.9 (1.5–5.1)	4.1 (1.9–5.4)	0.011
Comorbidities, *n* (%)			
Chronic pulmonary disease	5 (4%)	3 (2%)	0.183
Hypertension	59 (47%)	25 (13%)	< 0.001
Diabetes	42 (33%)	18 (9%)	< 0.001
Coronary artery disease	13 (10%)	4 (2%)	0.002
ASA class of ≥ 3, *n* (%)	93 (74%)	121 (63%)	0.052
Diagnosis, *n* (%)			
Chronic pancreatitis	73 (58%)	171 (90%)	< 0.001
Acute pancreatitis	13 (10%)	14 (7%)	
Benign neoplasm	40 (32%)	6 (3%)	< 0.001
Concurrent procedure, *n* (%)			
Splenectomy	55 (44%)	146 (76%)	< 0.001
Gastrectomy	10 (8%)	0	< 0.001
Lymphadenectomy	3 (2%)	2 (1%)	0.351
Operative time, min, median (range)	310 (75–1140)	530 (370–1007)	< 0.0001

TP, total pancreatectomy; IAT, islet cell auto-transplantation; ASA, American Society of Anesthesiologists.

preoperative weight loss of >10% of body weight than patients in the TP group (Table 1). Although these data are not necessarily clinically significant, median albumin was higher among TP + IAT patients compared with TP patients (4.1 g/dl versus 3.9 g/dl; $P = 0.011$). Hypertension, diabetes and coronary artery disease were more prevalent among TP patients ($P < 0.002$).

Outcomes

The primary outcome, major morbidity, occurred in 115 (36%) patients. These events occurred more frequently in patients undergoing TP + IAT compared with those submitted to TP alone [$n = 79$ (41%) versus $n = 36$ (29%); $P = 0.02$]. Multivariable logistic regression was conducted to adjust for baseline differences in patient age, preoperative weight loss, hypertension, ASA class of ≥3, and transfusion of ≥2 units of red blood cells (RBCs). The model showed that TP + IAT was associated with an increase of 96% in the odds of major morbidity [95% confidence interval (CI) 1.1–3.5; $P = 0.020$]. However, Hosmer–Lemeshow testing of the regression showed poor model fit ($P = 0.0002$), which suggests that this model may not explain the outcome well. Despite a narrow confidence interval and statistical significance, the adjusted analysis should be interpreted with this caveat.

The two groups experienced the same incidence of minor complications ($n = 60$, 19%). The multivariable model included the following covariables: age; ASA class of ≥3; transfusion of ≥2 units of RBCs, and diabetes. Performance of TP + IAT was not associated with increased odds of minor morbidity on logistic regression [odds ratio (OR) 0.98, 95% CI 0.5–1.9; $P = 0.950$]. Hosmer–Lemeshow testing showed goodness of fit ($P = 0.609$).

There was a trend towards higher overall morbidity in the TP + IAT group. Although the difference was not statistically significant, 48 (38%) patients in the TP group and 93 (49%) patients in the TP + IAT group suffered some morbidity ($P = 0.063$).

Analysis of the secondary outcomes showed no difference in mortality, surgical site infection or shock (Table 2). Myocardial infarction and cardiac arrest were sufficiently rare in both groups as to obviate valid statistical comparison. Postoperative pneumonia, septic and VTE complications were slightly higher in the TP + IAT group, but the differences were not statistically significant ($P > 0.05$). Transfusions were substantially more frequent after TP + IAT [$n = 39$ (20%) versus $n = 9$ (7%); $P = 0.001$]. Patients who underwent TP + IAT required longer hospitalizations (13 days versus 9 days; $P < 0.0001$).

Subset analysis

The predetermined subset excluded patients undergoing resection for benign tumours in order to focus on those with the best established indication for TP + IAT, namely, pancreatitis. As

Table 2 Postoperative morbidity in the study population ($n = 317$)

	TP group $n = 126$ (40%)	TP + IAT group $n = 191$ (60%)	*P*-value
Death, *n* (%)	3 (2%)	1 (1%)	0.147
Any morbidity, *n* (%)	48 (38%)	93 (49%)	0.063
Major morbidity, *n* (%)	36 (29%)	79 (41%)	0.020
Minor morbidity, *n* (%)	24 (19%)	36 (19%)	0.965
Surgical site infection, *n* (%)	21 (17%)	33 (17%)	0.887
Venous thromboembolism, *n* (%)	4 (3%)	11 (6%)	0.289
Pneumonia, *n* (%)	7 (6%)	20 (10%)	0.125
Re-intubation, *n* (%)	4 (3%)	7 (4%)	0.815
Failure to wean, *n* (%)	8 (6%)	12 (6%)	0.981
Transfusion, *n* (%)	9 (7%)	39 (20%)	0.001
Sepsis, *n* (%)	16 (13%)	28 (15%)	0.621
Shock, *n* (%)	3 (2%)	2 (1%)	0.351
LoS, days, median (range)	9 (3–120)	13 (4–195)	< 0.0001

TP, total pancreatectomy; IAT, islet cell auto-transplantation; LoS, length of stay.

Table 3 Postoperative morbidity in the subset of patients with pancreatitis only ($n = 271$)

	TP group $n = 86$ (32%)	TP + IAT group $n = 185$ (68%)	*P*-value
Death, *n* (%)	3 (3%)	1 (1%)	0.061
Major, *n* (%)	24 (28%)	76 (41%)	0.036
Minor, *n* (%)	19 (22%)	34 (18%)	0.473
Wound, *n* (%)	13 (15%)	31 (17%)	0.733
Pneumonia, *n* (%)	6 (7%)	20 (11%)	0.319
VTE, *n* (%)	4 (5%)	10 (5%)	0.794
Transfusion, *n* (%)	6 (7%)	38 (21%)	0.005
Sepsis, *n* (%)	11 (13%)	27 (15%)	0.691
Shock, *n* (%)	3 (3%)	1 (1%)	0.061
LoS, days, median (range)	10 (3–120)	13 (4–195)	0.006

TP, total pancreatectomy; IAT, islet cell auto-transplantation; VTE, venous thromboembolism; LoS, length of stay.

expected based on the findings shown in Table 1, this reduced the TP group in size ($n = 86$) to a greater extent than it did the TP + IAT group ($n = 185$). The study findings were unchanged; TP + IAT was associated with increased rates of major morbidity ($P = 0.036$) and transfusion ($P = 0.005$) (Table 3). This group continued to have a significantly longer hospital stay ($P = 0.006$).

Discussion

The pain caused by chronic pancreatitis is associated with substantial reductions in quality of life. Although it is not a panacea, TP can provide pain relief. Studies show marked improvements in physical and mental domains on instruments measuring quality of life, as well as decreased narcotic use.[8–10] Total pancreatectomy is reserved for refractory patients because of the risks for postoperative diabetes and persistent pain. The combination of TP + IAT, which is a very different procedure, has implications for perioperative morbidity.

The present data show a 50% higher rate of major morbidity, a nearly three-fold rate of transfusion, and a longer length of stay in patients undergoing TP + IAT compared with those undergoing TP alone. Differences between the procedures may explain this. To avoid warm ischaemia to the islet cells during TP + IAT, vascular ligation is performed later than in TP, and this is likely to increase blood loss. In addition, major peritoneal haemorrhage is one of the more common complications after islet cell transplantation. These factors and the systemic anticoagulation used during TP + IAT are likely to result in higher perioperative blood loss and transfusion rates. Although the individual differences are not statistically significant, higher rates of VTE, pneumonia and sepsis, when aggregated, are likely to explain the substantially higher major morbidity in TP + IAT.

Despite higher major morbidity, mortality was not significantly worse in TP + IAT patients. Selection bias, demonstrated by baseline differences in patient age and comorbidities, may explain this. Gusani *et al.*[11] showed that perioperative mortality was predicted well by a model that included only preoperative risk factors, which was minimally improved by the addition of further parameters. Alternatively, TP + IAT is only performed at large institutions that are likely to have the capacity to rescue patients who experience major complications.[12]

Postoperative hepatic insufficiency may explain the longer hospitalizations of TP + IAT patients. Islet transplantation registry data demonstrate that transient hepatic insufficiency is not uncommon.[13] Portal hypertension or hepatic ischaemia may occur through the occlusion of portal venules by infused islet cells. This is invariably self-limited. However, this theory cannot be tested as the NSQIP does not assess postoperative hepatic function.

Overall, the findings of the present study are consistent with data reported in the existing literature. Current series of TP alone report perioperative morbidity rates of 36.5–39.0%.[5,6,14] Similar series of TP + IAT have shown morbidity in 58–69% of patients.[3,15] This literature also supports the present authors' conclusion that TP + IAT may be associated with higher morbidity. The uniform data collection of the NSQIP across multiple centres allows for the direct comparison of outcomes between TP alone and TP + IAT.

The indication for TP + IAT has generally been chronic pancreatitis. However, there is a small group of patients in whom benign tumours require TP. In a recent series, patients with pancreatic body or neck tumours received IAT.[16] These data show that TP + IAT is performed, albeit rarely, in patients with benign neoplasia. However, as the clearest indication for TP + IAT is pancreatitis, this group was examined separately. The results of the subgroup analysis mirrored those in the larger population, which adds robustness to these findings.

The limitations of the present study arise from the dataset and the study's retrospective design. In this study, 60% of patients underwent TP + IAT, which implies that centres performing this procedure are over-represented in the NSQIP. However, if the experience of centres expert in TP + IAT demonstrates higher morbidity despite the selection of healthier patients, the morbidity attendant on TP + IAT must be higher. In addition to selection bias, there remains the possibility that patients in whom IAT was performed after a delay may be miscategorized under the TP rather than the TP + IAT group.

This study compared the perioperative morbidity associated with TP + IAT and TP, respectively, but does not support any comment on the benefits of either treatment. A review of the current literature demonstrates that IAT may mitigate the severity of insulin-dependent diabetes, but should not be thought of as preventing its occurrence. Over time, rates of type 2 diabetes drop substantially from 46% at 5 years, declining to 10% at 8 years.[17] However, even if patients do not have type 2 diabetes, their average daily insulin use may be lower after TP + IAT than after TP alone.[1] Longterm studies demonstrate declining graft function and increasing insulin use.[18] The true benefit of IAT may lie in the reduction of hypoglycaemic episodes, but these data are rarely reported.[19] This benefit must be set in the context of perioperative morbidity. Previously, data on the risks of TP + IAT were limited to single-institution series and did not compare outcomes with those of TP.

Conclusions

Total pancreatectomy is the last resort for patients whose chronic pancreatitis has failed to respond to all other treatments. Despite being effective for symptoms, TP results in endocrinopathy. Surgeons considering TP should discuss referral to centres which perform TP + IAT with patients. However, TP + IAT may only mitigate endocrinopathy after whole-gland resection. Surgically, TP + IAT is a very different procedure and data on perioperative morbidity are limited. This study is the only prospective, multicentre study to have compared the perioperative outcomes of TP with those of TP + IAT. These data demonstrate higher rates of major morbidity and transfusion requirements, and longer hospitalizations in patients undergoing TP + IAT. In this relatively rare procedure with significant potential for patient benefit, better longterm outcomes data and large prospective series demonstrating perioperative outcomes may improve patient counselling and surgeon referrals. In the interim, for surgeons performing TP without IAT, this study should better inform patient discussions regarding the risks associated with referral for TP + IAT.

Conflicts of interest

None declared.

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