ORIGINAL ARTICLE

Relaparotomy for a pancreatic fistula after a pancreaticoduodenectomy: a comparison of different surgical strategies

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Abstract

Introduction: A relaparotomy for a pancreatic fistula (PF) after a pancreaticoduodenectomy (PD) is a formidable operation, and the appropriate treatment of anastomotic leakage is under debate. The objective of this study was to compare the outcomes of different strategies in managing the pancreatic remnant during a relaparotomy for PF after a PD.

Methods: In this retrospective study on prospectively collected data, 669 PD were performed between 2004 and 2011. The study group comprised 31 patients requiring a relaparotomy, because of delayed haemorrhage ($n = 19$) or sepsis ($n = 12$). The pancreatic stump was treated either using pancreas-preserving techniques (simple drainage or duct occlusion) or completion of a pancreatectomy (CP). In 2008, autologous islet transplantation (AIT) was introduced for endocrine tissue rescue of CP.

Results: The mortality rate, blood loss and transfusion requirement were similar for all techniques. Patients undergoing a CP required a further relaparotomy less frequently than patients with pancreas preservation (7% versus 59%, $P < 0.01$), and the intensive care unit (ICU) stay was reduced after CP ($P = 0.058$). PF persisted at discharge in 66% of patients after pancreas-preserving techniques. AIT was associated with CP in 7 patients, of whom one died post-operatively. Long-term graft function was maintained in four out of six surviving patients, with one insulin-independent patient at 36 months after transplantation.

Conclusions: When a PF requires a relaparotomy, CP has become our favoured technique. AIT can reduce the metabolic impact of the procedure.

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Introduction

A pancreaticoduodenectomy (PD) remains one of the more challenging abdominal operations. Although mortality rates have reduced during the past 30 years owing to centralization to high-volume centres,[1] the overall morbidity still reaches 60%.[2] The most serious complications, such as late post-operative haemor-

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rhage and sepsis, derive mainly from a post-operative pancreatic fistula (PF) from a leaking pancreatic anastomosis. In spite of previous studies claiming outstanding results in reducing leakage rates, with almost no need for reoperation,[3] the actual rate of a severe (grade C) PF requiring a relaparotomy varies between 5% and 20%[2] even in experienced centres, with a mortality rate as high as 39%.[4] During a relaparotomy, different intra-operative strategies have been described, including both preservation of the pancreatic remnant and a completion pancreatectomy (CP).[5] Pancreas-preserving approaches are technically easier than CP

and have the advantage of maintaining pancreatic function but they expose patients to the risk of further complications as a result of a persistent PF. CP is a technically demanding operation that inevitably leads to complete pancreatic insufficiency, characterized by a complex diabetic condition named 'brittle' diabetes.[6]

The objective of this retrospective analysis was to compare the outcomes of different strategies in managing the pancreatic stump during a relaparotomy for PF after a PD.

Patients and methods

Data were collected prospectively in an electronic pancreatic surgery database and analysed retrospectively.

All procedures were carried out by experienced surgeons who had completed a training programme in pancreatic surgery.[7] The pancreatic anastomosis was performed in all patients as a two-layer end-to-side pancreatico-jejunostomy on the proximal jejunal limb. In the presence of risk factors for pancreatic anastomosis leakage (soft pancreas, small pancreatic duct or both), the pancreatic anastomosis was fashioned on a separate Roux-en-Y jejunal limb. Prophylaxis with octreotide (0.1 mg three times a day) was started in all patients on the day of surgery, continued until post-operative day 7 in case of a high-risk anastomosis and prolonged until discharge in case of PF.

One 28-French gauge tubular drain was placed routinely on the posterior side of the pancreatico-jejunostomy. An extra drain was placed on the anterior side in the event of a high-risk anastomosis. Since 2010, flat Penrose drains were used instead of tubular drains.

All patients were treated according to an enhanced recovery after surgery protocol.[8] Post-operative complications were defined according to our previous study.[9] The severity of post-operative complications was graded according to Clavien–Dindo classification,[10] which was validated in pancreatic surgery.[11] Complications graded as III to V were considered as major. A PF was defined according to the International Study Group for Pancreatic Surgery criteria.[12]

In the event of a delayed post-operative haemorrhage, if the patient was haemodynamically stable the treatment algorithm included a diagnostic contrast-enhanced CT scan, followed by interventional radiology with embolization or stenting for active arterial bleeding. A relaparotomy was performed when there was haemodynamic instability, failure to identify a source of bleeding or failure of angiographic treatment. A relaparotomy was performed when sepsis was associated with a peripancreatic fluid collection not amenable to percutaneous drainage, or after failure of percutaneous drainage.

Techniques of pancreatic stump treatment during a relaparotomy

Pancreatic stump management during a relaparotomy included three different techniques. Of the two preserving the pancreatic stump, the first consisted of debridement and drainage of the peripancreatic region (defined as simple drainage), the other through the occlusion of the main pancreatic duct by prolamine injection (Ethibloc®; Ethicon, Norderstedt, Germany), after resecting the dehiscent jejunal loop previously anastomosed to the pancreas. Prolamine was no longer available in our Institution from September 2008. The third technique consisted of a CP, with removal of the distal pancreas and splenectomy.

In most cases, the choice of the technique relied on the surgeon's preference, but in other cases it was forced by the patient's conditions or intra-operative findings: patient's severe haemodynamic instability forced a pancreas-preserving technique, because critical conditions ruled out the possibility of major surgery such as a CP; intra-operative findings of necrotic pancreatitis associated with leakage made CP mandatory; and tough visceral adhesions preventing access to the pancreatic stump, especially in case of delayed re-operation, excluded the possibility of CP.

To reduce the potential bias because of non-homogeneous patients undergoing a relaparotomy, the instances when there was no possibility to choose between a pancreas-preserving technique and CP were excluded from the study group.

In November 2008, autologous islet transplantation (AIT) was introduced for endocrine-tissue rescue in case of CP. Exclusion criteria for AIT were: pre-operative diabetes and the presence of neoplasia in the pancreatic stump including a benign neoplasm such as a multifocal intraductal papillary mucinous neoplasm. In contrast, the diagnosis of malignancy in the previously removed pancreatic head was not considered a contraindication for AIT if frozen-section examination of the resection margin was normal. The isolation process was performed as previously described.[13,14] Islets were usually infused in the portal vein, by interventional radiology through a percutaneous transhepatic approach the day after surgery or by the surgeon during the relaparotomy (one case). When patient instability did not allow an angiographic procedure, intra-bone marrow transplantation was performed (two cases).

Outcome measures assessed included mortality, the need for a further relaparotomy or interventional radiology, intensive care unit (ICU) duration of stay, blood loss and transfusion requirement, length of stay, persistence of PF at discharge and onset of diabetes.

Statistical analysis

Data are shown separately for each of the three different techniques. The outcomes of SD and DO (pancreas-preserving techniques) were grouped for comparison versus CP. Descriptive data are reported as mean (standard deviation), median (range) or number of patients and percentage. Categorical variables were compared using the chi-square test, continuous variables by the Student's t-test and non-parametric Mann-Whitney U-test.

Results

Between 1 January 2004 and 31 December 2011, 669 PD were performed. Characteristics of the patients are listed in Table 1. In

Table 1 Baseline and intra-operative data of the entire cohort

	All patients (*n* = 669)
Age (years)	64.6 (11.2)
Gender:	
Male	397 (59%)
Female	272 (41%)
BMI (kg/m²)	23.4 (5.2)
Diabetes	191 (29%)
Insulin therapy	63 (9%)
ASA score:	
Grade I	59 (9%)
Grade II	495 (74%)
Grade III	115 (17%)
Cancer	528 (79%)
Pre-operative chemotherapy	34 (5%)
Jaundice	470 (70%)
Haemoglobin serum levels (g/dl)	12.8 (1.5)
Operative time (min)	399 (82)
Operative blood loss (ml)	573 (362)

BMI, body mass index; ASA, American Society of Anesthesiologist.
Data are number of patients (%), or mean (standard deviation).

Table 2 Post-operative outcome of the entire cohort

	All patients (*n* = 669)
Mortality	29 (4%)
Complications	
Patients without complications	243 (37%)
Grade I–II	303 (45%)
Grade III–V	123 (18%)
Pancreatic fistula	201 (30%)
Grade A	103 (15%)
Grade B	61 (9%)
Grade C	37 (6%)
Readmissions	43 (6%)
Length of hospital stay (days)	16.8 (12.7)

Data are number of patients (%), or mean (standard deviation).
Complications graded according to Clavien–Dindo classification.

336 patients (50.2%) the anastomosis was fashioned on a separate Roux-en-Y jejunal limb, owing to the presence of risk factors for leakage. Table 2 shows the post-operative outcome of the entire cohort in detail. A clinically relevant PF (grade B–C) occurred in 98 patients (14.6%); 37 (5.5%) underwent a relaparotomy (grade C) and comprised the study group. Indications for relaparotomy were: delayed haemorrhage (22 patients, 59.5%) and sepsis (15 patients, 40.5%).

Between 2004 and 2011, 37 patients underwent a relaparotomy for pancreatic leakage after PD. Six of these patients were excluded

from the study as a result of intra-operative impossibility of choosing between a pancreas-preserving technique and a CP: two of these patients had necrotic pancreatitis of the stump and mandatorily underwent CP, two were in a critical condition, unfit for major surgery and in two further patients, the pancreatic stump was inaccessible. Thus, the study population included 31 patients.

During a relaparotomy 17 patients (55%) underwent a pancreatic-preserving procedure: 10 patients (32%) were treated with simple drainage (SD) of the anastomotic region and 7 patients (23%) with pancreatic duct occlusion (DO) with prolamine. The remaining 14 (45%) patients underwent a CP. Since 2008, nine of these patients were candidates for AIT and seven (78%) successfully received AIT. The other two patients were excluded owing to severe bacterial contamination of the islet solution in one instance and because of haemodynamic instability in the other.

The median post-operative day of relaparotomy was day 13, and was similar in the three groups, with no difference in the cause of relaparotomy between the groups. Table 3 shows patient characteristics at the time of relaparotomy.

Operative time and intra-operative blood loss were significantly higher in patients treated with CP. However, a significantly higher number of patients treated using pancreas-preserving techniques required extra reoperations (10 patients, 59% versus 1 patient, 7%). These further reoperations were mainly because of relapsing haemorrhagic complications, which were more frequent in patients with pancreatic stump preservation. Considering the whole post-operative course, including all further relaparotomies, overall blood loss was not different between the groups with an overall similar transfusion volume.

Overall mortality was 25.8%, and did not differ between the groups. The causes of mortality were multiple organ failure in five patients, respiratory failure in two patients and hemorrhagic shock in one patient. In patients treated by CP, only one of 11 patients (9.1%) has died since 2008. Post-operative morbidity was similar between the groups (Table 4). More patients were admitted to the ICU after a CP, but the mean ICU stay per patient was higher in patients in whom the pancreas was preserved. This seemed to be related to the persistence of sepsis or haemorrhagic relapse.

Hospital length of stay (LOS) after a relaparotomy was slightly lower in patients undergoing CP compared with pancreas-preserving procedures. The mean LOS was 22.4 compared with 34.4 days (*P*-value = 0.103). This difference may reflect the higher number of post-operative sequelae in the group of patients who received a pancreas-sparing procedure. In this group, 8 out of 12 of the surviving patients (66%) had a persistent PF at the time of discharge.

Patients who underwent AIT received a mean number of 1806 ± 513 equivalent islets per kilogram of body weight. AIT-associated complications occurred in two patients (29%): one patient had a septic exacerbation minutes after islet infusion; in another patient with sepsis, transient portal thrombosis was observed.

Table 3 Patients characteristics at the time of relaparotomy

	Pancreas preservation (n = 17)		Completion pancreatectomy	P-value
	Simple drainage (n = 10)	Duct occlusion (n = 7)	(n = 14)	
Age (years)	72.1 (11.9)	64.5 (12.0)	59.7 (6.5)	0.236
Gender: male/female	6/4	7/0	12/2	0.517
Pre-operative diabetes	1 (10%)	2 (29%)	1 (7%)	0.385
Cancer	7 (70%)	4 (57%)	10 (71%)	0.690
ASA score:				0.871
Grade III	4	3	6	
Grade ≥ IV	6	4	8	
Cause of relaparotomy				0.979
Haemorrhage	6	4	9	
Sepsis	4	3	5	
Day of relaparotomy	13 (4–32)	14 (5–24)	17 (6–42)	0.465

ASA, American Society of Anesthesiologist.
Data are number of patients (%), or mean (standard deviation), or median (range).
P-values are referred to pancreas-preserving procedures versus completion pancreatectomy.

Table 4 Intra- and post-operative outcome of relaparotomy

	Pancreas preservation (n = 17)		Completion pancreatectomy	P-value
	Simple drainage (n = 10)	Duct occlusion (n = 7)	(n = 14)	
Operative time (min)	122 (35)	193 (71)	240 (72)	**0.001**
Operative blood loss (ml)				
First relaparotomy	961 (809)	916 (816)	2507 (1976)	**0.009**
All relaparotomies	3294 (3123)	1583 (829)	2514 (1979)	0.928
Overall transfusions (ml)	2841 (1857)	2719 (1632)	2376 (2399)	0.580
Mortality	3 (30%)	2 (29%)	3 (21%)	0.610
Patients requiring a further relaparotomy	7 (70%)	3 (43%)	1 (7%)	**0.003**
Total number of reoperations	8	4	1	**0.001**
Bleeding complications	4 (40%)	3 (43%)	2 (14%)	0.101
Bile leakage	1 (10%)	3 (43%)	3 (21%)	0.889
Delayed gastric emptying	4 (40%)	3 (43%)	5 (36%)	0.756
Medical complications	4 (40%)	3 (43%)	3 (21%)	0.242
Wound infection	2 (20%)	1 (14%)	6 (43%)	0.124
ICU stay				
Patients admitted to ICU	5 (50%)	3 (43%)	12 (86%)	**0.025**
Days of ICU stay	4.7 (6.0)	14.9 (32)	3.5 (2.9)	0.058
Hospital stay (days) after relaparotomy	35.5 (23.7)	32.9 (25.4)	22.4 (13.7)	0.103

ICU, intensive care unit.
Data are number of patients (%) or mean (standard deviation).
P-values are referred to pancreas-preserving procedures compared with a completion pancreatectomy.

At long-term follow-up, insulin-dependent diabetes was more frequent in patients treated with CP (10/11, 91% versus 5/12, 42%, $P = 0.017$). In the group of patients who received AIT (mean follow-up: 967 days, median follow-up: 930 days, range: 417– 1311); one patient died of post-operative hemorrhagic relapse 6 days after CP and transplantation; one patient was insulin-free until death occurring 36 months after AIT; 3 patients have insulin-dependent diabetes with a maintained graft function (C-peptide >

0.3 ng/ml); and 2 patients had loss of function of the graft (C-peptide < 0.3 ng/ml) and experienced brittle diabetes.

Discussion

A relaparotomy for PF after a pancreaticoduodenectomy is a dramatic operation; the patient is often in a critical condition and high blood loss is expected (about 1000–2500 ml in the present study) with the risk of damaging the biliary or digestive anastomoses. In this scenario, the crucial surgical choice relates to the preservation of the pancreatic remnant. Compared with a CP, there are several theoretical advantages in preserving the pancreas: it is an easier technique, with less blood loss and shorter operative time. However, the greatest advantage in preserving the stump is the avoidance of brittle diabetes that invariably follows a CP.[6] The quality of life in patients after a total pancreatectomy has been reported to be similar to patients with diabetes with different aetiology.[15] However, hypoglycemia-related mortality and complications, such as nephropathy, neuropathy and retinopathy, should be taken into consideration, especially in young patients with benign disease with a long-life expectancy.[15–17]

Several techniques have been proposed to maintain the pancreas during a relaparotomy for PF: drainage of the anastomotic region, preservation of a small pancreatic remnant, over sewing of the stump or duct occlusion with fibrin sealant,[18] pancreatico-gastrostomy[19] and the bridge stent technique.[20] Two of them (simple drainage and duct occlusion) were applied in the present study. Compared with SD, duct occlusion is associated with the resection of the dehiscent jejunal loop, should allow the conversion of an 'activated' PF into a 'pure' PF, avoiding the mixing of pancreatic enzymes with bilio-enteric secretions. However, the potential advantages of DO were not confirmed by our findings, as the two techniques had similar outcomes. In spite of the theoretical advantages of pancreas preservation, this choice was related to a high risk of persistent PF after relaparotomy. In this setting, PF may predispose to further haemorrhagic or septic episodes that could be fatal in these compromised patients. After pancreas-preserving techniques, 10 out 17 patients (59%) required a further relaparotomy after the first one (with two CP at second relaparotomy), whereas only one out of 14 patients (7%) treated primarily by CP needed a further operation. The high rate of a second relaparotomy also caused further blood loss after the first re-operation, so that, in spite of the significant higher blood loss of a CP during the first relaparotomy, the overall blood loss and blood transfusion volume were similar between the different approaches. A similar observation can be made for ICU stay. The number of patients admitted to ICU was higher after CP, owing to the major impact of the procedure, but overall ICU stay was shorter for patients after CP, and the difference was close to significance (0.058). In spite of a reduction in the relaparotomy rate and ICU stay, mortality was not significantly reduced in the CP group, although in the last 11 patients treated with this approach it was 9%.

To encompass the problem of brittle diabetes after CP, islet auto-transplantation has been seldom reported[21,22] but has been employed successfully since 2008 in our institution. Insulin independency was achieved only by one of the six patients surviving the operation (16.7%). However, in spite of the need for insulin therapy, graft function was maintained in the other three patients, so that AIT avoided brittle diabetes in four out of six patients of this subgroup.

The main limitation of the present study, as well as similar reports comparing different strategies during relaparotomy for PF, is the lack of homogeneity of the study group, as patients requiring a relaparotomy may be quite different in terms of clinical condition and intra-operative findings. We tried to reduce this selection bias, excluding patients in whom there was no possibility to choose between pancreas preservation and CP, owing to critical conditions, anatomic findings or pancreatic necrosis.

In conclusion, CP has become the technique of choice in our experience when reoperation for PF is needed, as in most cases it is the definitive operation, avoiding the persistence of activated pancreatic juice in the operative field. In patients treated with CP, the association with AIT can reduce the metabolic consequences of the procedure.

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