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Risk factors, predictors and prevention of pancreatic fistula formation after pancreatoduodenectomy

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Abstract
Background/Purpose. Although the operative mortality and morbidity associated with pancreatoduodenectomy (PD) has been decreasing, pancreatic fistula remains a potentially fatal complication. The aim of this study was to identify risk factors and predictors of pancreatic fistula formation, and ways to prevent this in a consecutive series of PD patients in a single institution.
Methods. The association between pancreatic fistula formation and various clinical parameters was investigated in 50 patients who underwent PD at Kochi Medical School from January 1991 through February 2006.
Results. The incidence of pancreatic fistula in these patients was 28%. Multivariate analysis identified three independent factors correlated with the occurrence of pancreatic fistula: (1) absence of fibrotic texture of the pancreas examined intraoperatively (relative risk [RR], 1.6; 95% confidence interval [CI], 1.2–2.0; $P = 0.01$); (2) serum amylase concentration greater than 195 U/l (1.69 times the normal upper limit) on the first postoperative day (RR, 2.4; 95% CI, 1.0–5.7; $P = 0.01$); and (3) not having early postoperative enteral nutrition (RR, 3.2; 95% CI, 1.2–9.0; $P = 0.004$).
Conclusions. Soft texture of the pancreas and increased serum amylase the day after PD are both risk factors with predictive value for pancreatic fistula. The incidence of fistula formation is reduced by early postoperative enteral nutrition.

Key words Pancreatoduodenectomy · Pancreatic fistula · Surgery · Complication · Pancreas

Introduction

The operative mortality associated with pancreatoduodenectomy (PD) has declined to less than 5% in recent years.[1,2] However, among the postoperative complications of PD, which also include anastomotic leakage, intraabdominal abscess, and wound infection,[3–5] pancreatic fistula remains especially problematic, with its significant risk of a fatal outcome.[6–11] Although various strategies to reduce the incidence of pancreatic fistula have been proposed and tested, the incidence of pancreatic fistula associated with pancreatic surgery still ranges from 5% to 35%, even at high-volume institutions.[6,12–16]

The aim of this study was to identify risk factors that might assist in predicting the occurrence of pancreatic fistula following PD. We compared patients who developed pancreatic fistula with those who did not, in a series of PD patients from a single institution. The clinical parameters analyzed included various patient characteristics, indicators of pancreatic status, and operation-related risk factors. In addition, we evaluated the role of early postoperative enteral nutrition in the prevention of pancreatic fistula.

Subjects and methods

Patients

The study population comprised 51 patients who underwent PD for mass lesions in the pancreatic head, from January 1991 through February 2006, at Kochi Medical School. The final diagnoses for these patients were: pancreatic invasive ductal carcinoma ($n = 21$), cholangiocarcinoma ($n = 12$), carcinoma of the papilla of Vater ($n = 7$), intraductal papillary mucinous neoplasms ($n = 6$), mass-forming chronic pancreatitis ($n = 3$), carcinoid of the duodenum ($n = 1$), and metastatic tumor from renal cell carcinoma ($n = 1$). One of the 51 patients (who had cholangiocarcinoma) developed hepatic failure without pancreatic fistula and died 9 days after surgery, yielding an overall mortality rate of 2.0% following PD in our series. This patient was excluded and a total of 50 patients were enrolled in this study.

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For all patients a history of the presenting illness was obtained and a complete physical examination was performed. A self-administered questionnaire was used to gain information about their smoking and drinking habits, and details of their previous medical history (e.g., malignancies in other organs, diabetes mellitus, hypertension, cardiovascular disease, or respiratory disease). The body mass index was calculated by dividing the body weight in kilograms by the square of the height in meters. Laboratory tests included serum amylase and lipase levels, determined before PD and on the first postoperative day. Abdominal computed tomography was performed preoperatively for each patient, to assess the mass in the pancreatic head and the underlying status of the pancreas.

Operative procedures

In accordance with the preferences of the operating surgeons, 30 patients (60%) underwent pylorus-preserving PD and 20 (40%) underwent standard PD. In all patients, the pancreas was reconstructed first, followed by reconstruction of the hepatic duct and the duodenum or stomach. During the operation, the pancreatic parenchyma was assessed for fibrotic texture, and the pancreatic parenchyma and the main pancreatic duct were measured at the surgically transected surface of the pancreas. The pancreatico-enteric anastomosis was performed as a pancreaticojejunostomy in an end-to-side fashion. Total tube drainage of the pancreas was placed through the pancreatico-enteric anastomosis, which enabled us to monitor the daily output of pancreatic juice. The following parameters were evaluated as potential operation-related risk factors for pancreatic fistula: modification of PD (standard PD versus pylorus-preserving PD), duration of the operation, estimated intraoperative blood loss, intraoperative transfusions, method of pancreatic transection (whether or not an ultrasonically activated scalpel was used), and intraoperative radiotherapy.

We also evaluated early postoperative enteral nutrition, which was started on the day after the surgery via a catheter placed into the jejunum.[17] The incidence of pancreatic fistula in these patients was compared to that in patients with late postoperative enteral nutrition, who received total parenteral nutrition for at least 1 week and then started oral nutrition.[17]

Pancreatic fistula

A pancreatic fistula was considered to be present when both of the following criteria were fulfilled: (1) the concentrations of amylase and lipase in the drainage fluid from the tube inserted around the pancreatico-enteric anastomosis were three times higher than those in the serum; and (2) the drainage volume was more than 10 ml a day. Both the amylase concentration and the volume of the drainage fluid were examined on postoperative days 1, 3, 4, 5, and 7, and twice a week thereafter.[18–20]

Statistical analysis

Differences were evaluated using the χ^2 test, Fisher's exact test, and the *t* test. Multivariate analysis was used to identify independent factors correlated with pancreatic fistula. Receiver operator characteristic curve analysis was employed to obtain optimal cutoff values for (1) estimated intraoperative blood loss, and (2) serum amylase level on the first postoperative day. Where appropriate, values are expressed as means + SD. $P < 0.05$ was considered significant.

Results

Univariate analysis

Of the 50 patients who underwent PD for a mass lesion in the pancreatic head, 14 (28%) fulfilled the criteria for pancreatic fistula. The comparison of clinical characteristics and concurrent diseases between these patients and those without pancreatic fistula is shown in Table 1. There were no significant differences between the two groups in age, sex, body mass index, smoking habit, or habitual alcohol intake. In addition, there were no significant differences in the prevalence of concurrent or previous diseases.

Parameters indicative of pancreatic status were compared for patients with and without pancreatic fistula (Table 2). Of the parameters analyzed, the only significant difference between the two groups was in the occurrence of fibrotic texture of the pancreatic parenchyma, as evaluated during the operation ($P = 0.01$). Notably, none of the 14 patients with pancreatic fistula were assessed as having a fibrotic texture of the pancreas, whereas it was present in 13 (36%) of the 36 patients without fistula. It was also noteworthy that there was no significant difference between the two groups in the diameter of the main pancreatic duct at the surgically transected surface of the pancreas.

The findings for the operation-related parameters that we evaluated as potential risk factors for pancreatic fistula are summarized in Table 3. The estimated intraoperative blood loss in patients with pancreatic fistula (1214 ± 600 ml) was significantly higher than that in patients without pancreatic fistula (852 ± 355 ml; $P = 0.01$). Receiver operator characteristic curve analysis indicated the optimal cutoff value for estimated blood loss to be 825 ml, yielding a sensitivity of 64.3% and a

Table 1. Clinical characteristics and concurrent diseases

	Parameter	Pancreatic fistula		*P*
		Present	Absent	
Clinical characteristics	Age (years)	66.9 ± 11.4 (*n* = 14)	68.9 ± 9.1 (*n* = 36)	0.51
	Sex, male	9/14 (64%)	22/36 (61%)	0.91
	Body mass index	21.9 ± 3.1 (*n* = 14)	21.7 ± 3.1 (*n* = 36)	0.86
	Smoking	5/14 (36%)	17/36 (47%)	0.68
	Habitual alcohol intake	7/14 (50%)	17/36 (47%)	0.89
Concurrent diseases	Diabetes mellitus	6/14 (43%)	17/36 (47%)	0.97
	Hypertension	4/14 (29%)	15/36 (42%)	0.60
	Cardiovascular disease	4/14 (29%)	8/36 (22%)	0.92
	Respiratory disease	5/14 (36%)	7/36 (19%)	0.40
	Cancer in other organs	5/14 (36%)	11/36 (31%)	0.99

Table 2. Parameters indicative of pancreatic status

	Pancreatic fistula		*P*
	Present	Absent	
Serum amylase (U/l; normal, 40–115)[a]	215 ± 318 (*n* = 14)	167 ± 195 (*n* = 36)	0.52
Serum lipase (U/l; normal, 13–60)[a]	82 ± 76 (*n* = 3)	150 ± 267 (*n* = 24)	0.67
Fat replacement of the pancreas[b]	5/14 (36%)	16/36 (44%)	0.81
Fibrotic texture of the pancreas[c]	0/14 (0%)	13/36 (36%)	0.01
Size of the pancreatic parenchyma[d]	16.6 ± 4.6 (*n* = 14)	14.7 ± 4.4 (*n* = 36)	0.18
Diameter of the main pancreatic duct[d]	2.6 ± 1.4 (*n* = 14)	3.6 ± 2.4 (*n* = 36)	0.14

[a] Examined before the operation
[b] Based on preoperative computed tomography
[c] Evaluated during the operation
[d] Evaluated at the surgically transected surface of the pancreas during the operation

Table 3. Operation-related risk factors and postoperative management

Characteristics	Pancreatic fistula		*P*
	Present	Absent	
Pylorus-preserving PD	6/14 (43%)	24/36 (67%)	0.22
Operation time (min)	490 ± 106 (*n* = 14)	504 ± 96 (*n* = 36)	0.65
Estimated blood loss (m)	1214 ± 600 (*n* = 14)	852 ± 355 (*n* = 36)	0.01
Intraoperative transfusion	9/14 (64%)	13/36 (36%)	0.14
Method of pancreatic transection[a]	5/14 (36%)	22/36 (61%)	0.19
Intraoperative radiotherapy	2/14 (14%)	11/36 (31%)	0.41
Early enteral nutrition	3/14 (21%)	25/36 (69%)	0.02
Serum amylase (U/l; normal, 40–115)[b]	1255 ± 2454 (*n* = 14)	210 ± 271 (*n* = 36)	0.01

PD, pancreatoduodenectomy
[a] Use of ultrasonically activated scalpel
[b] Measured on the first postoperative day

specificity of 58.3% for the occurrence of pancreatic fistula (Fig. 1).

No significant differences were found between the two groups in the rates of pylorus-preserving PD, duration of the operation, intraoperative blood transfusion, method of pancreatic transection (conventional surgical division versus transection using an ultrasonically activated scalpel), or intraoperative radiotherapy.

However, the patients with fistula had a significantly lower rate of early enteral nutrition following the operation, with only 21% (3/14) of these patients having received it, compared to 69% (25/36) of the patients without fistula ($P = 0.02$).

In addition, the mean serum amylase concentration, measured on the first postoperative day, was significantly higher in patients with fistula (1255 ± 2454 U/l)

than in patients without fistula (210 ± 271 U/l; $P = 0.01$). Receiver operator characteristic curve analysis of the serum amylase level for the occurrence of pancreatic fistula indicated an optimal cutoff value of 195 U/l, which is 1.69 times the normal upper limit. According to this analysis, serum amylase concentrations greater than this cutoff value 71.4% sensitivity and 69.4% specificity for the prediction of pancreatic fistula (Fig. 1).

Daily outputs of pancreatic juice were monitored for 2 weeks postoperatively and compared in patients with and without fistula (Fig. 2). The pancreatic juice production in patients with fistula tended to be higher than that in patients without fistula, but the differences were not significant.

Multivariate analysis

The four parameters revealed by the univariate analysis to be significantly different between the fistula and non-fistula patient groups were further analyzed by multivariate logistic regression (Table 4). This resulted in three of the parameters being identified as independent factors correlated with the occurrence of pancreatic fistula: (1) absence of fibrotic texture of the pancreatic parenchyma (relative risk, 1.6); (2) serum amylase level more than 195 U/l on the first postoperative day (relative risk; 2.4); and (3) postoperative management without early enteral nutrition (relative risk, 3.2). The estimated intraoperative blood loss was not associated with a significant increase in relative risk.

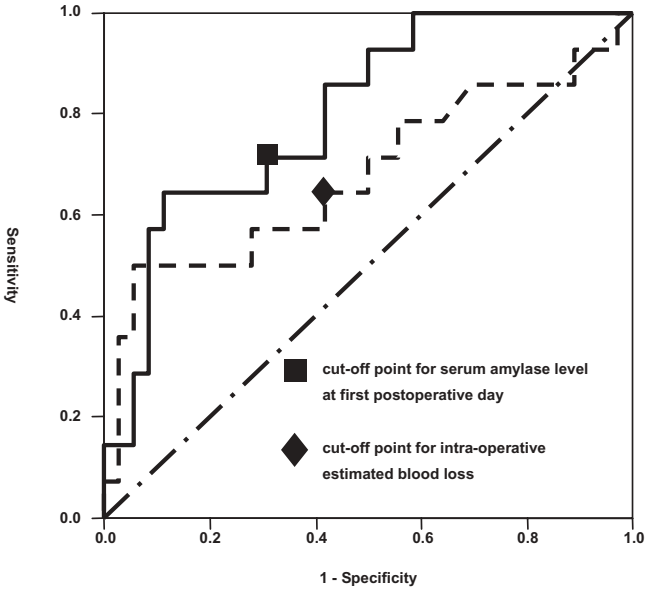

Fig. 1. Receiver operator characteristic curve analysis for intraoperative estimated blood loss and serum amylase concentration on the first postoperative day

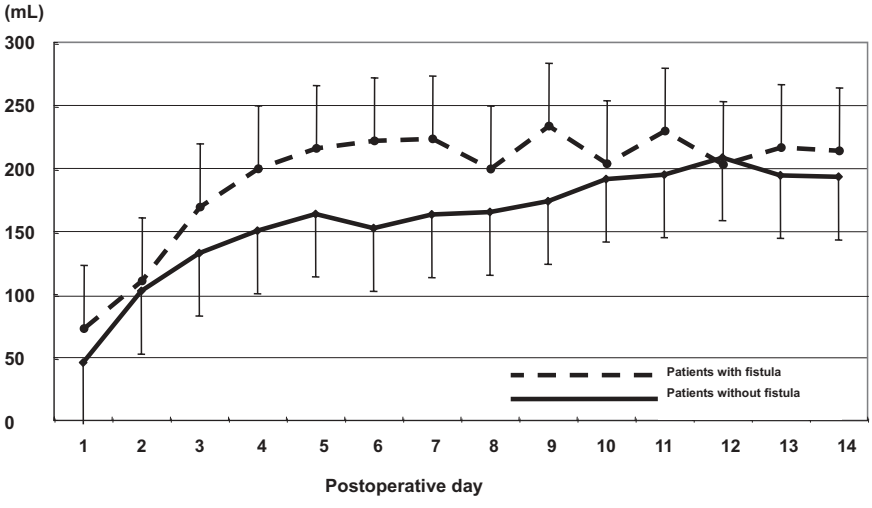

Fig. 2. Daily pancreatic juice output

Table 4. Multivariate analysis of risk factors for pancreatic fistula

	Relative risk (95% CI)	*P*
Fibrotic texture of the pancreas	1.6 (1.2–2.0)	0.01
Serum amylase (>195 U/ml)[a]	2.4 (1.0–5.7)	0.01
Not having early enteral nutrition	3.2 (1.2–9.0)	0.004
Estimated blood loss (>825 ml)	0.6 (0.4–1.1)	0.21

CI, confidence interval
[a] Measured on the first postoperative day

Discussion

A limited number of studies about pancreatic fistula have been reported, with incidence rates showing a wide range (5%–35%);[12,13] this wide range is probably due to the lack of general consensus on the clinical definition of the entity. In previous studies, pancreatic fistula was diagnosed in patients fulfilling the following criteria; (1) a high amylase level in the abdominal drain effluent (more than three times the serum level); (2) leakage proven by computed tomography, ultrasonography, and/or relaparotomy; (3) one or more clinical signs indicating peritonitis, such as progressive abdominal pain, body temperature above 38.5 °C, or leucocytosis above 15×10^9 cells/l.[21] When these criteria were applied in our series of PD patients, the incidence of pancreatic fistula was 5.9%. In the present study, we applied a rigorous definition of pancreatic fistula, with criteria for amylase and lipase concentrations in the drainage fluid that were relative to serum concentrations, and with a specified minimum daily volume of drainage fluid.[16,18–20] Accordingly, the incidence of pancreatic fistula established in our series (28.0%) is consistent with reports from other high-volume centers.[6]

In our analysis of a consecutive series of PD patients from a single institution, we identified three independent risk factors with predictive value for pancreatic fistula. The first of these was the absence of fibrotic texture of the pancreas, which has also been reported as a risk factor in previous studies.[22–24,27,28] Table 5 shows a review of previous studies that evaluated risk factors for pancreatic fistula by multivariate analysis. Interestingly, four of the seven studies, including the present one, indicated soft pancreatic texture as an independent risk factor, with a wide range of relative risks (1.6–15.4). This risk factor might be explained by the ability of a firm and fibrotic pancreatic remnant to hold sutures securely.[22,23,27] It is also possible that the limited exocrine function of a fibrotic pancreas makes it less likely to induce leakage of pancreatic juice. This is consistent with our observation that the daily output of pancreatic juice, which is the most reliable parameter for exocrine pancreatic function, tended to be lower in patients without pancreatic fistula (although the differences were not significant). Furthermore, it has been reported that the incidence of pancreatic fistula is decreased with pancreatic duct diameters larger than 2 or 3 mm (Table 5).[22,23] Such dilated ducts are a typical consequence of occlusive pancreatitis, and the fibrotic texture of the pancreas associated with this condition might therefore account for the reduced risk of fistula formation after PD.

In contrast to previous reports,[22,23] our study failed to show that a smaller diameter of the main pancreatic duct was a risk factor for pancreatic fistula. There is some evidence that a narrower main pancreatic duct carries a higher risk of occlusion of the pancreaticoenteric anastomosis.[29] A possible reason for this discrepancy between our findings and the previous ones is that, for all our patients, pancreaticojejunostomy was performed in an end-to-side fashion with total tube drainage. Other reports have suggested that duct-to-mucosa anastomosis for pancreaticojejunostomy may instead be a superior procedure for maintaining long-term patency of the anastomosis and for conserving pancreatic function.[24] However, the results of the present study indicate that total tube drainage is a safe method that can be applied in patients with narrower main pancreatic ducts.[25]

The second parameter that we identified as a risk factor for pancreatic fistula was the serum amylase concentration measured on the first postoperative day. This finding is not surprising, because an increase in serum amylase frequently occurs when a pseudocyst develops following acute pancreatitis.[30] The high serum amylase associated with the pseudocyst may result from an increase in tissue pressure due to pooling of the leaked pancreatic juice, which then induces a backflow from the pseudocyst into blood vessels. A similar mechanism is likely to occur in cases of pancreatic fistula; thus, in patients with an increased level of serum amylase just after the operation, the administration of antiprotease agents could help to prevent or treat pancreatic fistula.

The third parameter that was associated with an increased risk of fistula in our study was postoperative management without early enteral nutrition. Conversely, this indicates that early enteral nutrition was associated with a reduced incidence of fistula, and our findings therefore support the use of early enteral nutrition in patients who underwent PD.[17] In a previous study, we compared clinical outcomes in patients who underwent PD and were then either managed with early enteral nutrition (enteral feeding starting on the day after surgery) or late enteral nutrition (starting 7–14 days after surgery).[17] In that study, early enteral nutrition was associated not only with a decreased incidence of pancreatic fistula but also with sustained serum concentrations of total protein and albumin, maintenance of body mass index, early restoration of peripheral lymphocyte numbers, and a shorter length of hospitalization. Together, these findings suggest that early enteral nutrition following PD benefits the patient's nutritional status, resulting in favorable healing of the pancreaticojejunostomy and a significantly lower incidence of pancreatic fistula.

Previous studies with multivariate analysis have suggested additional risk factors or predictors correlated with an increased rate of pancreatic fistula, including long operation time,[25,26] underlying coronary artery

Table 5. Review of studies evaluating risk factors of pancreatic fistula after pancreatoduodenectomy by multivariate analysis

Reported year	*n*	Pancreatic fistula (%)	Independent factors Relative risk (95% confidence interval), *P* value				Reference no.
			Soft pancreatic texture	Small diameter of the MPD	Long operation time	Others	
2003	141	22 (15.6)	3.2 (1.3–8.2), $P < 0.01$	NS	NA	—	22
2004	1891	216 (11.4)	10.0 (2.1–47.6), $P = 0.004$	NA	NS	Coronary artery disease 3.73 (1.2–12.1), $P = 0.03$	23
2004	129	16 (12.4)	8.3 (Not reported), $P = 0.02$	NA	NS	Pancreatic duct ligation 2.1 (not reported), $P = 0.05$[e]	24
2005	62	10 (16.1)	15.4 (1.6–146.5), $P = 0.017$	11.8 (2.0–71.9) $P = 0.007$[a]	NS	—	9
2005	149	27 (18.1)	NS	NS	3.7 (1.2–11.6) $P = 0.01$[c]	—	25
2005	459	41 (8.9)	NA	3.1 (1.5–6.4) $P = 0.002$[b]	2.3 (1.14–4.9) $P = 0.031$[d]	Ampullary cancer 2.7 (1.1–7.0), $P = 0.03$	26
Present study	50	14 (28.0)	1.6 (1.2–2.0), $P = 0.01$	NS	NS	Serum amylase 2.4 (1.0–5.7), $P = 0.012$[f] No use of EEN 3.2 (1.2–9.0), $P = 0.0044$	Present study

EEN, early enteral nutrition; MPD, main pancreatic duct; NS, not significant; NA, not analyzed
[a] MPD diameter <3 mm
[b] MPD diameter <2 mm
[c] Operation time >6 h
[d] Operation time >285 min
[e] Using fibrin glue
[f] First postoperative examination

disease,[23] pancreatic duct ligation using fibrin glue,[24] and ampullary cancer as an indication for PD[26] (Table 5). Among these factors, a long operation time was indicated in two studies, with relative risks of 3.7 and 2.3. However, three other studies failed to nominate it as a risk factor. In our study also, operation time was comparable in the patient groups with and without pancreatic fistula.

In conclusion, the incidence of pancreatic fistula was 28% in the present consecutive series of 50 PD patients from a single institution. Multivariate analysis comparing patients with and without pancreatic fistula identified three independent risk factors for fistula formation: (1) absence of fibrotic texture of the pancreas (i. e., a pancreas with soft or normal texture); (2) serum amylase concentration greater than 195 U/l on the first postoperative day; and (3) not having early postoperative enteral nutrition through the jejunostomy catheter. These findings should assist in predicting fistula formation in patients who undergo PD, and the results also support the use of early postoperative enteral nutrition as a means of reducing the incidence of pancreatic fistula in such patients.

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