Objective: To evaluate the risk factors for pancreatic fistula after pancreatic head resection.

Design: Retrospective review.


Patients and Intervention: Sixty-two patients who underwent pancreatic head resection with pancreatojunostomy. We performed an extensive analysis of preoperative and perioperative risk factors for pancreatic fistula.

Main Outcome Measures: Pancreatic fistula was defined as high amylase level (>1000 U/L) in the drainage fluid collected from the peripancreatic drains and/or anastomotic disruption demonstrated radiographically.

Results: Nine (15%) of the 62 patients developed pancreatic fistula, and 1 (1.6%) died of intra-abdominal hemorrhage related to the pancreatic fistula. A preoperative normal N-benzoyl-l-tyrosyl-p-aminobenzoic acid test result ($P=0.01$), soft or intermediate pancreatic consistency ($P=0.04$), duodenum-preserving pancreatic head resection for the normal exocrine pancreas ($P=0.002$), and a larger amount of postoperative pancreatic juice output ($P=0.02$) were significant risk factors for pancreatic fistula formation.

Conclusions: Careful attention should be paid to the preoperative exocrine pancreatic function, pancreatic consistency at surgery, and postoperative pancreatic juice output to predict and prevent pancreatic fistula after pancreatic head resection.

Arch Surg. 1998;133:1094-1098

Diagnosis and Clinical Status

A pancreatic fistula occurred in 9 (15%) of the 62 patients who had undergone pancreatic head resection. The diagnosis of pancreatic fistula was established by a high amylase level in the drainage fluid in 6 patients (67%) and by fistulography in 3 patients (33%), and was confirmed by reexploration in 2 patients. The first clinical sign of the pancreatic fistula was dis-
PATIENTS AND METHODS

This series was composed of 62 Japanese patients who had undergone pancreatic head resection with pancreatojejunostomy at our institution from January 1992 through November 1997. There were 38 men and 24 women, with a mean age of 61 years (range, 21-84 years). All patients had elective surgery after full workup and control of preoperative conditions. A standard PD was done in 11 patients, pylorus-preserving pancreatoduodenectomy (PPPD) in 43 patients, and duodenum-preserving pancreatic head resection (DPPHR) in the other 8 patients. Pancreatojejunostomy was performed in a 2-layer, end-to-side fashion with either a mucosa-to-mucosa anastomosis method (34 patients) or a total tube drainage method (28 patients). A pancreatic duct drainage tube was used in all patients. Between 2 and 4 Penrose drains were routinely placed in the vicinity of the pancreatic anastomosis. Of the 62 patients, 21 received 20- to 25-Gy intraoperative radiotherapy. The final histopathological diagnosis was pancreatic cancer in 15 patients, ampullary cancer in 11, distal bile duct cancer in 7, malignant endocrine tumor in 3, mucinous cystadenoma in 10, intraductal papillary adenoma in 7, serous cystadenoma in 2, and chronic pancreatitis in the other 7. Pancreatic fistula was defined as a high amylase level (>1000 U/L) in the drainage fluid collected from the peripancreatic drains and/or anastomotic disruption demonstrated radiographically, in combination with clinical signs such as abdominal pain, fever of greater than 38.0°C, or elevated leukocyte counts of greater than 15×10⁹/L.

The medical records were reviewed for the following 27 clinical variables: patient age, sex, diameter of the main pancreatic duct, the N-benzoyl-L-tyrosyl-p-aminobenzoic acid (BT-PABA) excretion test value, peripheral white blood cell counts, hematocrit, serum level of albumin, total bilirubin level, blood urea nitrogen level, amylase level, history of jaundice, presence or absence of diabetes mellitus, American Society of Anesthesiologists physical status score, type of operation (PD, PPPD, or DPPHR), operative time, blood loss during surgery, intraoperative blood transfusion, intraoperative radiotherapy, type of pancreatic anastomosis (mucosa-to-mucosa vs total tube drainage method), pancreatic texture in the operative findings (soft or intermediate vs hard), use of fibrin glue on the pancreatic anastomosis, malignant or benign diseases, histopathological diagnosis, presence or absence of lymph node metastasis, tumor involvement at the surgical margins, prophylactic administration of octreotide, and total pancreatic juice output for a relatively stable 10-day period (postoperative day 5-14).

The results of parametric data are expressed as means±SDs. A univariate analysis of risk factors associated with pancreatic fistula was performed using the χ² test, Fisher exact test, and Mann-Whitney U test. A logistic regression model was used to determine the effects of multiple factors on pancreatic fistula. P<.05 was considered significant.

RISK FACTORS

Preoperative risk factors are listed in Table 1. No significant differences were observed between the nonfistula and fistula groups with respect to the patients' age, sex, diameter of the main pancreatic duct, white blood cell count, hematocrit, serum level of albumin, total bilirubin level, serum urea nitrogen level, amylase level, history of jaundice, presence or absence of diabetes mellitus, and American Society of Anesthesiologists physical status score. Of the multiple preoperative parameters, the only factor that significantly affected the pancreatic fistula was a normal BT-PABA test value of 70% or higher (P=.01). Intraoperative parameters including operative time, blood loss during surgery, blood transfusion, and type of pancreatic anastomosis did not influence the rate of pancreatic fistula formation (Table 2). With regard to the type of operation, DPPHR significantly increased the risk of pancreatic fistula (P=.002). Notably, 4 patients who developed pancreatic fistula after DPPHR had normal preoperative BT-PABA values, while the other patients without fistula had low BT-PABA values. No significant differences between the 2 groups were observed for the incidence of malignant or benign pathological characteristics, histological diagnosis, presence or absence of lymph node metastasis, and tumor involvement at the surgical margins. Intraoperative radiotherapy and the prophylactic use of fibrin glue or octreotide provided no significant effect in preventing the pancreatic fistula formation. Patients with a soft or intermediate pancreatic texture had a significantly higher risk of pancreatic fistula than those with a hard consistency (P=.04). A postoperative parameter that significantly increased the risk of pancreatic fistula was larger pancreatic juice output from pancreatic drains (≥1000 mL) (P=.02).

TREATMENT AND OUTCOME

Six (67%) of the 9 patients were successfully treated conservatively, with maintenance of the peripancreatic drains placed intraoperatively, use of antibiotics, and intravenous hyperalimentation without oral intake. The other 3 patients developed further complications including intra-abdominal abscess (2 patients) and intra-abdominal hemorrhage (1 patient). Two patients required surgical intervention to control the pancreatic fistula, and were successfully managed by operative drainage in 1 patient and resection of the duodenum in the other. One patient who developed arterial hemorrhage from a pseudoaneurysm of the common hepatic artery died of multiple organ failure immediately after angiographic embolization. The patient had preliminary minor bleeding from the abdominal drains 4 days prior to major hemorrhage.

Table 1

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Nonfistula (N=32)</th>
<th>Fistula (N=15)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean±SD</td>
<td>Mean±SD</td>
<td>P= .01</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>%</td>
<td>%</td>
<td>P= .02</td>
</tr>
<tr>
<td>Diameter (mm)</td>
<td>Mean±SD</td>
<td>Mean±SD</td>
<td>P= .04</td>
</tr>
<tr>
<td>BT-PABA</td>
<td>Median</td>
<td>Median</td>
<td>P=.02</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Operation Type</th>
<th>Nonfistula (N=56)</th>
<th>Fistula (N=7)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD</td>
<td>%</td>
<td>%</td>
<td>P=.002</td>
</tr>
<tr>
<td>PPPD</td>
<td>%</td>
<td>%</td>
<td>P=.03</td>
</tr>
<tr>
<td>DPPHR</td>
<td>%</td>
<td>%</td>
<td>P=.002</td>
</tr>
</tbody>
</table>

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A multivariate logistic regression analysis regarding the 4 profound factors revealed that the type of operation was an independent risk factor ($t = 2.985$, $P \leq .01$).

In the present study, a pancreatic fistula occurred in 9 (15%) of the 62 patients who had undergone pancreatic head resection. One of the 9 patients died of arterial hemorrhage related directly to the pancreatic fistula. Thus, the associated mortality rate of the pancreatic fistula was 11%. A normal preoperative BT-PABA test value, soft or intermediate pancreatic texture, DPPHR, and larger postoperative pancreatic juice output were significant risk factors for pancreatic fistula formation following pancreatic head resection. Although the mortality rate in this series was not so high as those in previous reports from other institutions,6-10 pancreatic fistula and/or pancreatic anastomotic leakage is a serious complication that leads to a prolonged and complicated hospital stay.\(^\text{13}\)

In earlier studies, researchers evaluated several factors that predispose to pancreatic fistula formation after pancreatoenterostomy, ie, age older than 65 years, ampullary or duodenal disease, preoperative jaundice, soft or normal pancreatic parenchyma, small pancreatic duct, longer operative time, and higher-volume intraoperative blood transfusion.\(^\text{8-13}\) Of the above-mentioned parameters, soft or intermediate pancreatic texture significantly increased the risk of pancreatic fistula, whereas age, pathological characteristics, presence of jaundice, small pancreatic duct, operative time, and intraoperative blood transfusion did not influence the fistula formation in this series. However, we found other new risk factors.
factors including a normal preoperative BT-PABA test value and larger postoperative pancreatic juice output. Hamanaka et al\textsuperscript{11} reported that patients with pancreatic parenchyma of soft or intermediate consistency produced a larger amount of pancreatic juice and had a higher risk of pancreatic leakage than those with a hard consistency. The present study also supported their observations.

Since its introduction by Beger et al\textsuperscript{14} in 1985, DPPHR has been considered an alternative surgical technique in the treatment of chronic pancreatitis. This operation was claimed to provide effective pain relief and low postoperative mortality and morbidity when compared with other surgical procedures.\textsuperscript{15,16} At our institution, 8 patients with a benign cystic neoplasm confined to the head of the pancreas were treated by DPPHR. However, 4 patients (50\%) developed pancreatic fistula after surgery. In 1 of the 4 patients, the duodenum was resected at the second operation to control the pancreatic fistula. This high complication rate after DPPHR was probably due to an excessive exocrine secretion from the remnant pancreas attached to the duodenum, causing the pancreatic fistula formation. In fact, all 4 patients with pancreatic fistula had a normal preoperative BT-PABA value, while the other patients without fistula had a low value. Based on these observations, we believe that benign pancreatic disease without chronic pancreatitis would not be a good indication for DPPHR.

Many previous reports proposed a variety of anastomotic techniques to prevent pancreateojunostomy leakage, including the site of the jejenum (end vs side), type of anastomosis (mucosa-to-mucosa vs invagination), use of fibrin glue, and pancreatic duct stenting.\textsuperscript{17-21} However, the issue of the anastomotic technique is still controversial.\textsuperscript{22,23} No single method has proved to be satisfactory for all patients. Our policy throughout this period was to choose the end-to-side, mucosa-to-mucosa anastomosis method for a dilated pancreatic duct and the total tube drainage method for a nondilated pancreatic duct. However, there was no difference in the incidence of pancreatic fistula between the 2 anastomotic techniques in the present analysis.

Recently, prophylactic administration of octreotide has been reported to be effective to prevent pancreatic fistula and other postoperative complications after pancreatic surgery.\textsuperscript{24-26} However, in this study, octreotide provided no significant effect on the incidence of pancreatic fistula. In retrospect, 2 patients who were administered octreotide developed pancreatic fistula but were treated conservatively and did not develop intra-abdominal abscess or hemorrhage. These findings suggest that octreotide may lessen the risk of major leakage and further complications related to the pancreatic fistula. Ishikawa et al\textsuperscript{27} reported that preoperative irradiation prevented pancreatic fistula formation because of a putative decrease in the exocrine function at the anastomotic site. It is well known that exocrine pancreatic acinar cells are more radiosensitive than either islet or ductal cells, and that exocrine pancreatic insufficiency occurs after intraoperative radiotherapy.\textsuperscript{28} In the present study, however, intraoperative radiotherapy provided no significant benefit in preventing pancreatic fistula. This is partly explained by the fact that intraoperative radiotherapy only induces the exocrine deficiency long after surgery.\textsuperscript{28}

With regard to an optimal management of the pancreatic fistula, there has been no therapeutic modality established. In this series, 6 of the 9 patients with fistula were successfully treated conservatively. According to previous reports, initial treatment for pancreatic fistula is conservative, including simple maintenance of the peripancreatic drains placed intraoperatively and use of antibiotics and octreotide.\textsuperscript{6,7,9,29} However, when the patient develops intra-abdominal abscess, percutaneous or operative drainage is necessary because the regional sepsis erodes the major artery in the pancreatic bed and may cause life-threatening arterial hemorrhage. One of our 9 patients with pancreatic fistula developed major hemorrhage from a pseudoaneurysm of the common hepatic artery. Despite an immediate angiographic embolization, the patient died of multiple organ failure resulting from hemorrhagic shock. In retrospect, the patient had preliminary minor hemorrhage from the abdominal drains, the so-called sentinel bleed, 4 days prior to major bleeding.\textsuperscript{30} Our experience suggests that early detection of this sentinel bleed and a prompt response is mandatory in patients with a pancreatic fistula after pancreatectomy.

In conclusion, surgeons should pay attention to the preoperative exocrine pancreatic function, pancreatic consistency as an operative finding, and the volume of pancreatic juice output postoperatively when performing pancreatic head resection to prevent the pancreatic fistula.

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ARCHIVES OF INTERNAL MEDICINE

Effective Lipid Modification by Partial Ileal Bypass Reduced Long-term Coronary Heart Disease Mortality and Morbidity: Five-Year Posttrial Follow-up Report From the POSCH

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Background: In 1990, when the Program on the Surgical Control of the Hyperlipidemias (POSC) reported its in-trial results strongly supporting the conclusion that effective lipid modification reduces progression of atherosclerosis, the differences for the end points of overall mortality and mortality from atherosclerotic coronary heart disease (ACHD) did not reach statistical significance.

Methods: The Program on the Surgical Control of the Hyperlipidemias recruited men and women with a single documented myocardial infarction between the ages of 30 and 64 years who had a plasma cholesterol level higher than 5.69 mmol/L (220 mg/dL) or higher than 5.17 mmol/L (200 mg/dL) if the low-density lipoprotein cholesterol level was in excess of 3.62 mmol/L (140 mg/
dL). Between 1975 and 1983, 838 patients were randomized: 417 to the diet control group and 421 to the diet plus partial ileal bypass intervention group. Mean patient follow-up for this 5-year posttrial report was 14.7 years (range, 12.2-20 years).

Results: At 5 years after the trial, statistical significance was obtained for differences in overall mortality (P = .049) and mortality from ACHD (P = .03). Other POSCH end points included overall mortality (left ventricular ejection fraction ≥50%) (P = .01), mortality from ACHD (left ventricular ejection fraction ≥50%) (P = .05), mortality from ACHD and confirmed nonfatal myocardial infarction (<.001), confirmed nonfatal myocardial infarction (<.001), mortality from ACHD, confirmed and suspected myocardial infarction and unstable angina (<.001), incidence of coronary artery bypass grafting or percutaneous transluminal coronary angioplasty (<.001), and onset of clinical peripheral vascular disease (P = .02). There were no statistically significant differences between groups for cerebrovascular events, mortality from non-ACHD, and cancer. All POSCH patients have been available for follow-up.

Conclusion: At 5 years after the trial, all POSCH mortality and atherosclerosis end points, including overall mortality and mor-
tality from ACHD, demonstrated statistically significant differences between the study groups. (1998;158:1253-1261)

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