Management of Pancreatic Fistulas After Pancreaticoduodenectomy

Results in 437 Consecutive Patients

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Hypothesis: Pancreatic fistula (PF), a common and potentially lethal complication of pancreaticoduodenectomy, can be managed nonoperatively in most cases.

Design: Retrospective case series.

Setting: Major academic medical and pancreatic surgery center.


Interventions: Conservative management of PF with an intraoperatively placed closed-suction drain near the pancreaticojejunostomy anastomosis, computed tomography-guided percutaneous drainage, and surgery.

Main Outcome Measures: Incidence of PF after pancreaticoduodenectomy and patient outcomes.

Results: Fifty-five patients (12.6%) developed a PF, which was most common after resections for ampullary tumors (21.1%) and cystic neoplasms (31.3%), and uncommon after resection for pancreatic cancer (6.5%). The mean number of complications (excluding PF) was greater in the PF group (PF, 1.24; no PF, 0.54; P<.001), but these did not prolong hospital stay (PF, 15.2 days; no PF, 13.7 days; P=.20). Biliary fistula, sepsis, reoperation, and late biliary strictures were more common in patients with PF (P<.05), but mortality rate and long-term survival in patients with either pancreatic or ampullary cancer were unaffected by the presence of PF (P>.40). Fifty-two patients (94.5%) had successful conservative management of their PF with prolonged tube drainage; 4 also required CT-guided percutaneous drainage. Three patients (5.5%) underwent reoperation and 1 died.

Conclusions: Pancreatic fistula is a common problem after pancreaticoduodenectomy. It is associated with increased morbidity, but it does not affect the mortality rate. More than 90% of PF cases can be managed nonoperatively without significantly prolonging hospital stay.

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Pancreaticoduodenectomy (PD) has become an increasingly common and safe operation for selected patients with benign and malignant periampullary disorders. The operative mortality rates reported for many high-volume pancreatic surgical centers are now less than 5%, a dramatic improvement over the rate of 20% often reported during the 1970s. However, the postoperative morbidity rate is still 40% to 50%.1-4 Pancreatic fistula (PF) is the most problematic common complication after PD, and its reported incidence varies from 2% to 28%.1-13 Because many patients who developed PF in the past required reoperation and often died, much effort has been made to minimize its occurrence. This includes the use of the stomach instead of the jejunum for the pancreatic anastomosis, biological adhesives to seal the anastomosis, somatostatin analogues to inhibit pancreatic secretion, and a number of different surgical techniques to fashion the anastomosis. None of these methods have demonstrated a clear advantage.9,12-20 Therefore, prompt recognition and proper management of PF when it does occur are important. While many advocate conservative management of PF, some surgeons still favor aggressive surgical intervention.7,21 To further evaluate our own management strategies and experience with this problem, we conducted a retrospective study of the patients at University of California, Los Angeles.
Los Angeles (UCLA), Los Angeles, Calif, who developed PFs after PD. Data from patients who had distal pancreatectomy were not analyzed.

DATA COLLECTION

We reviewed the medical records of 437 patients who underwent PD for various indications at the UCLA Medical Center between January 1, 1988, and August 31, 2004. The review included patient demographics (age and sex), surgical data (type of resection, operative blood loss, and duration of surgery), pathological diagnosis (pancreatic adenocarcinoma, ampullary tumor, chronic pancreatitis, bile duct tumor, benign and malignant cystic neoplasms, intraductal papillary mucinous neoplasm, islet cell tumor, duodenal tumor, and others), postoperative morbidity and mortality rates, length of hospital stay, and long-term survival.

Patients were grouped according to whether they developed or did not develop a postoperative PF. A PF was defined as drainage of greater than 30 mL of amylase-rich fluid (at least 3 times the upper normal limit of serum amylase concentration) per 24 hours after the fifth postoperative day. Postoperative mortality was defined as death occurring in the first 30 postoperative days or before discharge from the hospital. For morbidity analysis, complications were categorized and their rates were compared between patients who developed a PF and those who did not. Delayed gastric emptying was defined as intolerance to oral intake and need for nasogastric decompression after the seventh postoperative day. Other complications were categorized and defined as any of the following: intraabdominal abscess (fluid requiring drainage and with positive bacterial culture); wound infection (purulent drainage requiring open packing); postoperative bleeding (requiring transfusion or endoscopic or operative intervention); bile leak (biliary drainage from intraoperatively placed drains or bile collection requiring drainage); biliary stricture (requiring stenting and/or late reoperation); cardiac (myocardial infarction or new-onset arrhythmia requiring intervention); pulmonary (pneumonia, effusion requiring drainage, or reintubation); sepsis (fever, leukocytosis, or bacteremia requiring medical and/or surgical intervention); and reoperation in the first 30 postoperative days or before discharge from the hospital. Follow-up data on long-term survival were obtained through medical record review, direct patient contact, and US Social Security Administration records.

METHODS

SURGICAL TECHNIQUE

Of the 437 resections, 356 (81.5%) were performed by 1 surgeon (H.A.R.), so variations in technique in the collected series were minimal. The operative approach for PD has been described elsewhere. We performed a standard lymph node dissection in all cases, which included clearance of the soft tissues and nodes along the right side of the superior mesenteric artery and anterior to the aorta. The pancreaticojunostomy was performed as a 2-layer anastomosis, where the inner layer incorporated the duct; pancreatic duct stents were not used. The hepaticojunostomy was performed as a single-layer anastomosis. For standard PD, an antrectomy was performed. For pylorus-preserving PD, the duodenum was transected 2 to 4 cm distal to the pylorus, and the right gastric artery was divided. Gastro-duodenaljunostomy was performed in a retrocolic position in most cases. Closed-suction drains (10-mm flat Jackson Pratt) were placed near the biliary and pancreatic anastomoses, and a T tube was used to stent the hepaticojejunostomy if the bile duct was less than 1 cm in diameter. Patients left the operating room with a nasogastric tube in place, which was removed the next morning.

PATIENT CHARACTERISTICS

From January 1, 1988, to August 31, 2004, 437 PDs were performed at the UCLA Medical Center for a variety of diagnoses (Table 1). Most of these were done for pancreatic adenocarcinoma (38.4%) or ampullary tumors (20.6%). Fifty-five patients (12.6%) developed a PF, with a median amylase level of 14 000 U/L (range, 913-11 000 U/L) in the abdominal drainage fluid. The likelihood of the development of a PF depended to a considerable degree on the underlying pathologic diagnosis. Rates of PF were lower for patients with pancreatic adenocarcinoma (11/168 [6.5%]) and chronic pancreatitis (1/36 [2.8%]) and higher for those with benign cystic neoplasms (5/16 [31.2%]), bile duct tumors (7/28 [25.0%]), and ampullary tumors (19/90 [21.1%]). However, univariate analyses demonstrated a significant increase in the chances of a PF after PD only in patients with benign cystic neoplasms (P<.05) and ampullary tumors (P<.01). Patients with pancreatic adenocarcinoma had a lower chance of the development of PF (P<.003). Pathological data are presented in Table 1.

The mean age of patients with PF (n=55) was 65.2 years, and of those without PF (n=382), 62.9 years (P=.20). Thirty-four (61.8%) of the patients with PF were male and 21 (38.2%) were female; 189 (49.5%) of the patients without PF were male and 193 (50.5%) were female (P=.09). Twenty-eight patients (50.9%) with PF had preoperative biliary stents and 178 patients (46.6%) without PF had biliary stents (P=.30). Demographic data are presented in Table 2.

OPERATIVE RESULTS

According to the preference of the operating surgeon, 294 patients (67.3%) underwent pylorus-preserving PD, and 143 (32.7%) underwent standard PD (Table 2). Of the
55 patients who developed a PF, 42 (76.4%) had undergone a pylorus-preserving PD. Thus, there was no significant difference in incidence of PF between the pylorus-preserving PD and standard PD groups \( (P = .20) \). Mean duration of operation was 6.9±0.1 hours for the no-PF group and 6.8±0.2 hours for the PF group. The mean operative blood loss was 493±29 mL for the no-PF group and 492±47 mL for the PF group. Neither the duration of operation \( (P = .60) \) nor the operative blood loss \( (P = .90) \) was significantly different in the 2 groups.

### POSTOPERATIVE OUTCOMES

There were 5 postoperative deaths for the entire series, an overall mortality rate of 1.1%. Four deaths occurred in the group without PF (1.0%) and 1 patient (1.8%) died in the PF group \( (P > .50) \). Postoperative complications, including PF, occurred in 206 of the 437 patients in the series, for an overall postoperative morbidity rate of 47.1%. The mean total number of complications for the group without PF was 0.54±0.04, compared with 1.24±0.15 \( (P < .001) \) for the group with PF, excluding PF itself. The mean length of hospital stay for the group without PF was 13.7±0.4 days; it was 15.2±1.1 days for the PF group \( (P = .20) \) (Table 2).

### Specific Postoperative Complications

Specific postoperative complication data are presented in Table 3. The most common other complications were delayed gastric emptying (PF, 20.0%; no PF, 13.9%; \( P = .30 \)), intra-abdominal abscess requiring drainage (PF, 12.7%; no PF, 5.8%; \( P = .08 \)), and wound infection (PF, 12.7%; no PF, 7.6%; \( P = .30 \)). Intra-abdominal bleeding occurred in 7.3% of patients with PF and 2.4% of patients without PF, but this difference did not reach statistical significance \( (P = .07) \). There were significant differences in rates of sepsis (PF, 7.3%; no PF, 1.8%; \( P < .05 \)), biliary fistula (PF, 9.1%; no PF, 0.5%; \( P < .001 \)), late biliary stricture (PF, 7.3%; no PF, 0.3%; \( P < .005 \)), and reoperation (PF, 5.5%; no PF, 1.0%; \( P < .05 \)).
To determine whether the development of PF after PD affected long-term patient survival, we analyzed the survival of patients in the series with pathologically confirmed pancreatic ductal adenocarcinoma (n=168) and ampullary adenocarcinoma (n=79). The Kaplan-Meier survival estimates for pancreatic adenocarcinoma (PF, 11 patients; no PF, 157 patients) and ampullary adenocarcinoma (PF, 15 patients; no PF, 64 patients) are presented in Figure 1 and Figure 2. The overall 5-year actuarial survival for patients with resected pancreatic adenocarcinoma and ampullary adenocarcinoma was 25% and 66%, respectively. The presence of PF did not influence long-term survival in either group (pancreatic adenocarcinoma, $P=.40$; ampullary adenocarcinoma, $P=.70$).

Advances in medical and surgical care have made PD a relatively safe operation, but it is still associated with significant morbidity, even in the most experienced hands. Pancreatic anastomotic fistula remains the most problematic and feared common complication. For that reason, we have analyzed our experience with PF during a 15-year period. The review represents one of the larger single-institution series, and it reflects modern methods of medical and surgical management. Because one surgeon performed more than three quarters of the resections, variability in surgical technique and management philosophy was minimal.

Fifty-five (12.6%) of the 437 patients in this series developed a PF after PD. There is still no consensus on a uniform definition of PF, and the broad range of PF rates reported in the literature (2%-28%) is largely a function of the definition used.23 For this review, we used the broad definition of daily drainage greater than 30 mL of fluid with an amylase concentration at least 3 times the upper normal limit of serum amylase concentration, from drains placed at surgery, after the fifth postoperative day.

In retrospect, all of our PF cases had drain amylase content at least 5 times the upper limit of normal. As we expected, the probability that a fistula would develop depended on the underlying disease for which the pancreatic resection was done. For example, PF was much more likely in patients who had benign cystic neoplasms ($P<.05$) and ampullary tumors ($P<.01$). In contrast, pancreatic adenocarcinoma was associated with a much lower rate of PF ($P<.003$). Other pathological diagnoses with higher rates of PF included intraductal papillary mucinous neoplasm, bile duct tumor, and islet cell tumor; however, these did not demonstrate a statistically significant association with PF, probably because of a limited sample size. Although we did not have specific information regarding the texture of the pancreas, the pathological trends observed support the conventional thinking that a soft pancreas is more likely to develop a PF than one that is firm and holds sutures more reliably.5

There were no apparent influences of age, type of PD (pylorus-preserving PD vs standard PD), duration of operation, or operative blood loss on the rates of PF formation. Although there was a preponderance of male patients (62%) in the group with PF, this did not reach statistical significance ($P=.09$). There are conflicting reports about whether placement of preoperative biliary stents increases the risk of PF.24-28 Sohn et al28 reported a review of 567 patients undergoing PD (1994-1997) and concluded that preoperative biliary stents increased the risk of PF and wound infection, but with no difference in overall morbidity and mortality. More recently, the same group reported an even larger series of 1739 patients accumulated for a longer time (1981-2002), which showed no difference in the rate of PF between patients who had preoperative stents and those who did not.5 Preoperative biliary stents were present in 47% of patients in our current series compared with 70% in the series described from Hopkins.5 We did not observe any statistical association between the presence of preoperative biliary stents and PF after PD ($P=.50$).
Pancreatic fistula remains a common problem after PD. Although it is associated with an increase in morbidity, we have not found that it affected postoperative mortality rates or long-term survival in patients with underlying pancreatic fistula. If there is no bile in the drainage fluid, the biliary drain is removed on the fourth or fifth postoperative day, when peristaltic activity returns and the patient begins receiving oral fluids. The pancreatic drain is removed only after the patient has begun a regular diet and the character of the drainage does not suggest a PF (cloudy or particulate fluid rather than water clear).

A high volume of drainage fluid (eg, 100-200 mL/24 h) itself is not a concern. This usually occurs on the eighth or ninth postoperative day, and the patient often is discharged after the drain is removed or on the following day. If there is any question about whether a fistula is present, fluid is sent for amylase determination. If there is a fistula, the patient can still be discharged home as long as he or she is eating and there is no evidence of sepsis. In the presence of fever or leukocytosis, we would obtain a computed tomographic scan to look for an intra-abdominal fluid collection, which would be drained percutaneously by interventional radiographic techniques. In our series, 52 (95%) of the 55 patients had conservative management of their PF with prolonged tube drainage; 4 of the 52 also required computed tomography–guided percutaneous drainage. After discharge, patients record their daily fistula output and are seen weekly in the office. At the first office visit, the suction bulb from the drain is removed, and the drainage tube is connected to a bag. This usually decreases the daily fistula output, and the fistula may close in a few days. If the fistula persists several weeks after discharge, we obtain a fistulogram and replace the original drain with a rubber catheter. This was done in 10 patients. Occasionally, the tip of the catheter is seen within the lumen of the bowel; of course, the replacement tube must be positioned more superficially. Then the fistula often closes within a day or so, and the drain is removed. We have never reoperated on a patient to close the fistula. We have not restricted oral intake, used parenteral nutrition as a specific treatment for the fistula, or used octreotide as an adjunct to management. Median postoperative time to removal of drains in the 52 patients treated in this way was 5 weeks (range, 2-14 weeks), and there were no deaths.

The remaining 3 patients with PF (5.5% of the total) underwent early reoperation. One had a peripancreatic retrogastric abscess that could not be drained by percutaneous techniques; 2 had sepsis that was complicated by hemorrhage, which was the reason for urgent surgery. Although suspected preoperatively, PF was diagnosed during surgery in these patients. At operation, the hemorrhage was controlled, the abscesses were drained, and all 3 patients underwent revision of their pancreaticojejunostomy and drain placement. Two of them required additional operative pancreatic debridement and drainage procedures. These patients had long and complicated hospital courses, and 1 died after progressing to multiorgan failure.

CONCLUSIONS
ing periampullary malignancy. Ninety-five percent of PF cases can be managed nonoperatively without significantly prolonging hospital stay. However, the occasional patient with inadequately drained intra-abdominal infection, which is often associated with PF, may need urgent reoperation. The challenge is to avoid this problem altogether or to recognize it earlier, so that these individuals may be treated more effectively.

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DISCUSSION

Lawrence W. Way, MD, San Francisco, Calif: In 1970 the mortality rate of Whipple operations was 15% to 20%, owing to pancreatic fistulas, bleeding, infection, and renal failure. Why was pancreatic fistula associated with such a high mortality rate? By itself a fistula is not life-threatening. The current study and others like it show that if infection and other complicating difficulties can be avoided, pancreatic fistulas produce little morbidity on their own. In fact, this is true of nearly all fistulas in the abdomen: gastric, biliary, small and large bowel, bladder, etc.

As stressed by Dr Reber and his coworkers, the key is to control the fistula. Place drains near the spot where the pancreas has been transected. Arrange them so they don’t get displaced. Use computed tomographic scans and fistulograms postoperatively to guide interventional radiology (IR) when IR involvement becomes necessary to improve fistulous drainage. Then the fistula will heal. Total parenteral nutrition is rarely indicated; one does not have to avoid stimulating the pancreas by fasting the patient. Dr Reber wrote an analogous paper (Ann Surg. 1978;188:460) over 25 years ago showing the success of these principles in the management of gastrointestinal fistulas.

Also of historical interest is an article that Dr Carlos Pellegrini and I published in 1989 (Arch Surg. 1989;124:778), ana...
lyzing the reasons for the sharp drop in the mortality rate (20% to approximately 2%) of Whipple operations over the preceding 20 years. One finding that stood out was the newfound ability to blunt the morbidity of pancreatic fistulas, which we attributed to the shift to closed-suction drains and the advent of IR techniques to drain undrained areas and to reposition malfunctioning drains. During the 1980s, we rarely found it necessary to reoperate in order to control a pancreatic fistula. But the current effort goes considerably beyond such previous insights to produce a comprehensive account of the prevention and management of postoperative pancreatic fistulas.

I have a few questions. First, how do you explain the good results reported from the Memorial Sloan-Kettering Cancer Center with the practice of avoiding the use of prophylactic drains after pancreatic resections? And second, what are your thoughts about ancillary techniques intended to prevent fistulas, such as pancreatic duct stents, intussusception of the pancreatic stump into the jejunum, pancreaticogastrostomy, tissue glue, or total pancreatectomy? Or is it reasonable to conclude from your findings that the regimen you follow is so effective that pancreatic fistulas are no longer the serious problems they once were? I agree in detail with your recommendations and congratulate you on an important and useful contribution. I believe it is the major article on pancreatic fistulas now and will continue to be for some time.

Lygia Stewart, MD, San Francisco: I just have a question to add to what Dr Way said. What are your thoughts on the utility of octreotide or Tisseel?

Bruce E. Stabile, MD, Torrance, Calif: I really enjoyed this paper, and the large volume of patient material allows us to learn some important lessons. I have no disagreement with the authors' approach or their conclusions. There have been a number of definitions of what truly constitutes a postoperative pancreatic fistula. The definition used here could just be a single day's output of greater than 30 mL of high-amylase-content fluid. I wonder if that really is a fistula in all cases. Certainly there have been cases in my own experience where the drain will not initially capture the fluid collection, and then several days later there is an outpouring of a relatively large volume, and a day or two later it's gone. I am not sure that is really a pancreatic fistula at all. Certainly any definition of a fistula, and I agree that any definition is arbitrary, I think that is a bit of an overstatement in the sense that the development of a fistula still carries with it significant risks for morbidity and for mortality as well. I think the real point is that if you are alert to their early diagnosis and if they are managed properly, then you can avoid an increase in the mortality rate. So I would not want to say that they are of relatively minor clinical importance. But if they are managed appropriately, I think that the great concerns that we used to have no longer are there.

Dr Stewart raised a question about, again, what I would describe as technical modifications to try to decrease the incidence of fistula. You mentioned a fibrin glue sealant, and I believe that a recent prospective study by the Hopkins group concluded that it made no difference at all. We have not used it, so I can't give you any personal experience with it.

Dr Stabile talked about a number of issues, including the definition of a fistula, and I agree that any definition is arbitrary. But our patients all left the hospital with significant fistula drainage (at least 50-75 mL/d) that persisted for at least a week or two, so this wasn't just a collection that evacuated itself and then stopped quickly.

You had a question about the association of fistulas and the underlying disease for which the resection was done. I think you are quite correct that the firmness of the pancreatic tissue varied according to the diagnosis, and that it was this that influenced the development of a fistula. Thus, in patients who had pancreatic duct obstruction, which is common with pancreatic cancer, and in those patients with chronic pancreatitis, the gland is firm, and the fistula rate is low. In those with ampullary cancer, the gland is usually soft, and many more develop a fistula.

Finally, you brought up the use of octreotide. We don't use it. As I am sure you know, there are a number of prospective randomized studies that have looked at its value. Several that have come from some of the European groups have concluded that it is of some value. Others from groups in this country have concluded that it isn't. I still remain unconvinced of its value.