Management of Pancreatic Fistulas After Pancreaticoduodenectomy

Results in 437 Consecutive Patients

Kevork K. Kazanjian, MD; Oscar J. Hines, MD; Guido Eibl, MD; Howard A. Reber, MD

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 stricture 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 peripancreatic 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,3,6,8 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, Department of Surgery, University of California, Los Angeles, Calif. CME course available at www.archsurg.com

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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.

STATISTICAL ANALYSIS

Data are presented as mean ± SEM unless otherwise indicated. Differences in the continuous variables of demographics, operative data, and length of hospitalization were analyzed by 2-tailed t tests. Differences in discrete demographic and operative variables were analyzed with Fisher exact test. Analyses of specific postoperative complications between the group with PF and the group without PF, as well as univariate analyses of specimen-related risk factors, were done with χ² tests. Differences in the overall complication rates between the PF group and the one without PF were analyzed with the Poisson binomial test. Survival estimates were generated by the Kaplan-Meier method, and survival curves were compared by means of the log-rank test. Statistical significance was achieved at P < .05. Statistical analyses were performed with SAS statistical software (SAS Institute Inc, Cary, NC).

RESULTS

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, 913-110,000 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 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).

Abbreviations: IPMN, intraductal papillary mucinous neoplasm; PF, pancreatic fistula.
pancreatic ductal adenocarcinoma and the influence of postoperative pancreatic fistula (PF). The 5-year postoperative actuarial survival rate for the entire cohort of 168 patients was 25% (PF, 11 patients; no PF, 157 patients). The presence of PF did not significantly influence survival (P = .43, log-rank test).

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).

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.

To determine 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.

COMMENT

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.
Previous studies reported that the development of PF after PD was associated with a greater number of other complications and prolonged the hospital stay. Indeed, our study demonstrated that in patients who develop a PF, the total number of complications in addition to PF was more than 2-fold that of patients without PF (1.24±0.15 vs 0.54±0.04; P<.001). On the other hand, the hospital stay was slightly, but not significantly, prolonged by the presence of the fistula (Table 2). This paradox can be explained by our comfort level with outpatient management of PF, whereas others may tend to continue inpatient management and observation for a longer period.

Postoperative complications occurred in 206 of the 437 patients in this series, for an overall postoperative morbidity rate of 47.1%, which is similar to the experience of others. The most common complications overall were delayed gastric emptying, PF, wound infection, and intra-abdominal abscess requiring drainage. Analysis of differences in specific postoperative complications between the PF and no-PF groups showed a significantly increased rate of biliary fistula, sepsis, reoperation, and late biliary stricture in the PF group (P<.001). On the other hand, the mortality rate of PD was 20% or more and many of the patients died because of the complications associated with a PF (eg, uncontrollable sepsis, intra-abdominal hemorrhage). The reasons for the difference are probably multiple. They include the current use of closed-suction drains and the ability to diagnose and treat promptly an inadequately drained fistula with computed tomography and modern interventional techniques. Likewise, we have shown that PD complicated by postoperative PF did not influence long-term survival in resected adenocarcinoma of the pancreas (25% at 5 years) or ampulla of Vater (66% at 5 years). This is of some interest because most patients with these underlying malignancies had the onset of their adjuvant therapy delayed until the fistula resolved. Nevertheless, the numbers of patients in these groups are too small to draw firm conclusions.

On the basis of our experience, we make the following recommendations for drain and fistula management. Despite recent recommendations to the contrary by one group of experienced surgeons,25 we continue to place one closed-suction Silastic drain (10-mm flat Jackson Pratt) anterior to the pancreaticojejunal anastomosis, and another posterolateral and to the right of the biliary-jejunal anastomosis. 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**

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 underly-
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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Correspondence: Howard A. Reber, MD, Division of General Surgery, UCLA School of Medicine, 72-215 CHS, 10833 Le Conte Ave, Los Angeles, CA 90095-6904 (hreber@mednet.ucla.edu).

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REFERENCES


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 that is ongoing but rather just a sequestered fluid collection that, when it occurs early, is always high in amylase. So the question is, did all of those patients who were defined initially capture the fluid collection, and then several days later there was no significant difference in fistula rate or morbidity. They then made the recommendation that we shouldn’t be using drains at all. I think that it would be wrong on the basis of that one study to draw any firm conclusions about this pancreatic fistula problem, which I think all of us over the years have come to view with such concern. I think that their results might be different with a larger number of patients in their series, and I would be very reluctant to stop using drains at this point. In my view, the question remains open.

Other techniques for the pancreatic anastomosis as a way of trying to minimize the frequency of pancreatic fistula is an approach that surgeons around the world have tried and continue to work with. Examples are the use of a pancreaticogastrostomy, or so-called dunking techniques for the pancreas, or the use of stents. I doubt that there are any technical modifications that we are likely to come up with that will decrease the frequency of fistulas below the point where they now are. The results that we presented today are good, but they are not unique. They are similar to the fistula rates that a number of experienced pancreatic surgeons around the world have been able to achieve, and they represent a number of different technical approaches. So I think that technical modifications are not likely to make much difference here. There was a period of time when I was experimenting with how to do the anastomosis better and for a number of years I used stents routinely. Then I stopped using stents and found that the incidence was no different at all. So for me at least, the use of stents for the anastomosis has not represented an improvement.

You suggested that maybe we now overrate the importance of fistulas because people generally don’t die if they have one. 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 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/4 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.