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RAPID COMMUNICATION

Risk factors associated with pancreatic fistula after distal pancreatectomy, which technique of pancreatic stump closure is more beneficial?

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Abstract

AIM: To identify risk factors related to pancreatic fistula in patients undergoing distal pancreatectomy (DP) and to determine the effectiveness of using a stapled and a sutured closed of pancreatic stump.

METHODS: Sixty-four patients underwent DP during a 10-year period. Information regarding diagnosis, operative details, and perioperative morbidity or mortality was collected. Eight risk factors were examined.

RESULTS: Indications for DP included primary pancreatic disease (n = 38, 59%) and non-pancreatic malignancy (n = 26, 41%). Postoperative mortality and morbidity rates were 1.5% and 37% respectively; one patient died due to sepsis and two patients required a reoperation due to postoperative bleeding. Pancreatic fistula was developed in 14 patients (22%); 4 of fistulas were classified as Grade A, 9 as Grade B and only 1 as Grade C. Incidence of pancreatic fistula rate was significantly associated with four risk factors: pathology, use of prophylactic octreotide therapy, concomitant splenectomy, and texture of pancreatic parenchyma. The role that technique (either stapler or suture) of pancreatic stump closure plays in the development of pancreatic leak remains unclear.

CONCLUSION: The pancreatic fistula rate after DP is 22%. This is reduced for patients with non-pancreatic malignancy, fibrotic pancreatic tissue, postoperative prophylactic octreotide therapy and concomitant splenectomy.

INTRODUCTION

Distal pancreatectomy (DP), first performed by Billroth in 1884, is defined as the resection of pancreatic tissue to the left of the superior mesenteric vessels. This procedure was infrequently performed in the past because the tumours of the pancreatic tail and body were often irresectable at the time of diagnosis and due to the general dissatisfaction with this procedure for the management of chronic pancreatitis. However, the advent and development of imaging and diagnostic techniques has increased the frequency of DP. Recently, the indications for DP include malignant and benign pancreatic diseases, non-pancreatic malignancies, chronic pancreatitis, and trauma.

Pancreatic fistula is the most common major complication after DP, ranging from 5% to 40%. Pancreatic leakage often leads to further complications, such as fluid collections or intra-abdominal abscesses, wound infections, respiratory complications, and sepsis[1]. The appropriate technique of closure the pancreatic stump is still under controversial[1,2]. The most common used techniques for closure of the transected pancreatic parenchyma and for prevention of pancreatic fluid extravasations from the residual pancreatic tissue are the hand-sewn parenchymal closure and the stapled closure.

The risk factors in the development of pancreatic fistula are also unclear. The method of pancreatic stump closure, malignancy, trauma, patient's age, concomitant splenectomy, or obesity are implicated as potentially important[3,4].

The purpose of this study was to determine possible risk factors that may be associated with the onset of pancreatic fistula after DP and to identify if the method of pancreatic stump closure plays a significant role in the

Table 1 Main parameters for postoperative pancreatic fistula grading[5]

Grade	A	B	C
Clinical conditions	Well	Often well	Ill appearing/bad
Specific treatment1	No	Yes/No	Yes
US/CT	Negative	Negative/Positive	Positive
Persistent drainage (after 3 wk)	No	Usually yes	Yes
Reoperation	No	No	Yes
Death related to fistula	No	No	Possibly yes
Signs of infection	No	Yes	Yes
Sepsis	No	No	Yes
Readmission	No	Yes/No	Yes/No

[1]Partial (peripheral) or total parenteral nutrition, antibiotics, enteral nutrition, somatostatin analogue and/or minimal invasive drainage.

development of pancreatic fistula.

MATERIALS AND METHODS

A retrospective review of 64 patients who underwent DP from January 1996 to December 2005 at the Department of Digestive Surgery, Gemelli University Hospital of Rome, was conducted.

Patients' age, sex, indications for surgery, concomitant splenectomy, additional procedures, methods of pancreatic stump closure, and postoperative complications with a specific focus on pancreatic leaks, mortality, and duration of postoperative hospital stay were recorded. Operative details also included operating time and the texture of pancreatic parenchyma. No patient was excluded from the series.

The indications for DP included either primary pancreatic diseases or non-pancreatic malignancies. All the operations were performed by same surgical team. Division of the pancreatic parenchyma was by knife or linear stapler (GIA), while the pancreatic remnant was either closed by a linear stapler or by hand running absorbable monofilament 3-0 sutures. One open drain was positioned near the transected pancreas and it was removed when the daily fluid output was lower than 10 mL or when amylase concentration in the fluid drain was unremarkable in cases of pancreatic leaks (< 300 IU).

We used prophylactic octreotide in the last 34 patients (53%), postoperatively for 7 d, while in cases with fistula the octreotide was prolonged until recovery. The dose of octreotide was 0.5 mg three times a day.

Postoperative mortality and morbidity were registered for 30 d or during the total hospitalisation time, if longer. Postoperative pancreatic leaks were classified according to the international accepted definition reported by Bassi *et al*[5] for the international Study Group on Pancreatic Fistula (Table 1). Suspicion and diagnosis of fistula based on biochemical criteria included drainage of more than 10 mL of fluid in 24 h, with an amylase content of more than 3 times the serum amylase activity (> 300 IU) for more than 10 d after surgery. The amount of fluid amylase collected from the drainage tubes, as well as the serum amylase level were evaluated daily until postoperative d 10, and longer in cases with pancreatic fistula. The clinical criteria included the presence of clinical symptomatology such as fever greater than 38℃, leucocytosis with peripheral white blood cells amount more than 10000 cells/mm^3, intra-abdominal pain or abscess, and the need of percutaneous drainage or reoperation. Intra-abdominal collections were detected by computed tomography (CT).

Oral feeding was generally started on second postoperative day in patients with insignificant amylase concentrations in the abdominal fluid collected by drainage or in patients with Grade A fistula. Conversely, patients with pancreatic fistula Grades B or C were kept with nothing by mouth and were supported with partial or total parenteral or enteral nutrition.

The following eight risk factors were analysed: age (patients older or younger than the age of 70 years old), gender, pancreatic disease or non-pancreatic malignancy, technique of pancreatic stump closure, spleenic preservation, texture of the pancreatic parenchyma (soft or fibrotic tissue), additional procedures, and postoperative use of octreotide. The texture of the pancreatic parenchyma was adequately defined by histopathology examination.

Statistical analysis

All data were reported as the mean ± standard deviation (SD) and/or median. The data were analyzed by means of SPSS 12.01 statistical package for Windows. Mann-Whitney *U* test and Chi-square test was used for group comparison and Students' *t* test to analyze normally distributed quantitative data. $P < 0.05$ was considered statistically significant.

RESULTS

All patients underwent DP for elective benign or malignant, pancreatic or non-pancreatic diseases. There were 30 males (47%) and 34 females (53%). The patients' age ranged from 42 to 84 years (median age, 72.3 years).

The indications for surgery included 38 patients (59%) with pancreatic disease and 26 patients (41%) with non-pancreatic malignancy. Forty-three patients (67%) underwent DP with splenectomy and one or more additional procedures due to primary malignancy: 17 of these patients (40%) had primary pancreatic malignancy infiltrated surrounding organs and 26 patients (60%) had non-pancreatic malignancy infiltrated pancreas. The overall number of additional procedures was 57. Spleen preserving DP was performed in 8 patients (13%); they all had benign or borderline diseases, while DP with splenectomy was performed in 13 patients (20%). The patients' demographics, indications for surgery, operative and technical factors are summarized in Table 2.

The median postoperative length of hospital stay, in patients without fistula, was 11 d (range, 6-15 d); while in patients with pancreatic fistula the median hospitalization was prolonged: 23 d (range, 16-28 d).

The postoperative mortality rate was 1.5% (one patient died due to sepsis), while the morbidity rate was 37% (n = 24). The patient with sepsis had both pancreatic and oesophago-jejunal fistula after total gastrectomy for cardiac cancer. The last 7 years no mortality rate occurred.

Table 2 Patients' demographics, indications for surgery, operative and technical factors

	No. of patients (%)
Sex	
Male	30 (47)
Female	34 (53)
Indications for surgery	
Pancreatic	
Cystadenoma	19 (30)
Adenocarcinoma	11 (17)
Neuroendocrine tumour	3 (5)
Cystadenocarcinoma	3 (5)
Chronic pancreatitis	1 (1.5)
Lymphangioma	1 (1.5)
Non-pancreatic	
Gastric adenocarcinoma	16 (25)
Retroperitoneal sarcoma	4 (6)
Colonic adenocarcinoma	2 (3)
Renal carcinoma	2 (3)
Adrenal grand carcinoma	1 (1.5)
Gastrointestinal stromal tumour	1 (1.5)
Operations	
DP + splenectomy	13 (20)
Spleen preserving DP	8 (13)
DP + splenectomy + additional procedure	43 (67)
Additional procedures	
Gastrectomy	26 (46)
Colon resection	12 (21)
Adrenalectomy	10 (17)
Small intestine resection	5 (9)
Nephrectomy	4 (7)
Closure of pancreatic stump	
Stapler	29 (45)
Suture	35 (55)

Table 3 Postoperative results

	No. of patients (%)
Death	1 (1.5)
Reoperation	2 (3)
Complications	
No	40 (63)
Yes	24 (37)
Pancreatic fistula	14 (22)
Grade A	4 (28.6)
Grade B	9 (64.3)
Grade C	1 (7.1)
Intra-abdominal hemorrhage	2 (3)
Intra-abdominal abscess	3 (5)
Pulmonary	5 (8)

Fourteen patients (22%) developed a pancreatic fistula; 4 of fistulas (28.6%) were classified as Grade A, 9 (64.3%) as Grade B and only 1 as Grade C (7.1%). Two patients (3%) required a second operation due to postoperative intra-abdominal bleeding. None of patients required a reoperation because of intra-abdominal abscess or fluid collection; these patients were treated by percutaneous drainage. Postoperative results are showed in Table 3.

Pancreatic fistula was significantly more common in patients who underwent DP for primary malignant or benign pancreatic diseases ($P = 0.04$) and in patients who did not receive postoperative prophylactic octreotide therapy ($P = 0.01$). Of 26 patients who were operated for non-pancreatic malignant disease, only 3 (11%) experienced a leak, compared with 11 (29%) of the 38 patients who were operated for pancreatic disease only. Four (12%) of 34 patients who received octreotide developed a pancreatic leak, compared with 10 (33%) of 30 patients who did not.

Table 4 Incidence of pancreatic fistula after distal pancreatectomy according to examined risk factors

		Fistula		
	Patients ($n = 64$)	No. ($n = 50$)	Yes ($n = 14$)	*P* value
Age (yr)				NS
< 70	23 (36)	17 (34)	6 (43)	
> 70	41 (64)	33 (66)	8 (57)	
Sex				NS
Male	30 (47)	23 (46)	7 (50)	
Female	34 (53)	27 (53)	7 (50)	
Pancreatic stump closure				NS
Stapler	29 (45)	22 (44)	7 (50)	
Suture	35 (55)	28 (56)	7 (50)	
Pathology				0.04
Pancreatic disease	38 (59)	27 (54)	11 (79)	
Non-pancreatic malignancy	26 (41)	23 (46)	3 (21)	
Octreotide therapy				0.01
Yes	34 (53)	30 (60)	4 (28)	
No	30 (47)	20 (40)	10 (72)	
Texture of pancreatic parenchyma				0.006
Soft	27 (42)	15 (30)	12 (86)	
Fibrotic	37 (58)	35 (70)	2 (14)	
Concomitant splenectomy				0.002
Yes	56 (87)	46 (92)	10 (71)	
No	8 (13)	4 (8)	4 (29)	
Procedures				NS
Pancreatic resection only	21 (33)	14 (28)	7 (50)	
Additional procedures	43 (67)	36 (72)	7 (50)	

NS: No significant. Values in parentheses are percentages.

The potential relationship between the texture of the pancreatic parenchyma and pancreatic leak was also evaluated, considering the remnant stump including resection margin: only 2 (5%) of the 37 patients with fibrotic pancreatic tissue experienced a leak, compared with 12 (44%) of the 27 patients with soft tissue ($P = 0.006$). Finally, we observed significant statistical difference comparing the patients who underwent concomitant splenectomy with them who did not: 10 (18%) of 56 patients with concomitant splenectomy experienced a pancreatic fistula, while 4 (50%) of 8 patients with spleen preserving procedure developed a pancreatic leakage.

The other factors such as age, gender, technique of pancreatic stump closure, and type of surgical procedures were not significantly associated with pancreatic fistula formation. The incidence of pancreatic fistula after DP according to the eight examined risk factors is summarized in Table 4.

DISCUSSION

In this report, we describe our 10-year experience with DP for pancreatic and non-pancreatic benign diseases and malignancies. Our findings identify the importance of four risk factors in the development of pancreatic fistula:

fibrotic pancreatic parenchyma, non-pancreatic disease, concomitant splenectomy, and postoperative prophylactic octreotide therapy were found to result in a statistically significant reduction in the rate of postoperative pancreatic leakage. No significant differences were found regarding to the onset of pancreatic fistula according to the rest of examined factors such as age, gender, technique of pancreatic stump closure, and additional procedures.

Mortality and morbidity after DP have significantly decreased the last decades[6]. In this study, we support that DP can be performed with low perioperative mortality (1.5%), while the incidence of pancreatic fistula, which was the most common postoperative complication, was 22%. These results are in accordance with the most authors' conclusions[3,4,7-9].

In the past, in most of published studies there was no definition of pancreatic fistula and the diagnostic criteria for this had not yet been completely established. Balcom *et al*[10] defined fistula as the drainage of more than 30 mL of amylase-rich fluid, while Balzano *et al*[4] used a strict definition of fistula: > 5 mL for five days after the fifth postoperative day. In this study, pancreatic leaks were classified according to the International Study Group on Pancreatic Fistula definition[5]. Grade A of pancreatic fistula, called transient fistula, has no clinical impact, Grade B requires a change in management or adjustment in the clinical pathway, while in Grade C, a major change in clinical management or deviation from the normal clinical pathway occurs. Our results showed that the majority of pancreatic fistulas were belonged to Grade B. These patients were supported with parenteral nutrition, the drains were maintained in place, some of them were covered by antibiotics and all were leaded to a delay in discharge. The only patient with Grade C fistula died postoperatively due to sepsis.

The appropriate closure of the pancreatic stump after DP in order to reduce postoperative complications, especially the incidence of pancreatic fistula, remains an unsolved surgical problem. A great number of surgical techniques and instruments for treating the resected pancreatic surface and preventing pancreatic fistula after DP has been proposed: hand-sewn suture[2,11,] stapler[1,2,7,11], a combination of stapler and suture[2,7,11], the use of pledgetted suture[7], fibrin-glue sealing[12,13], and prolamine injection[14]. The most commonly used techniques of pancreatic remnant management are the stapler and suture closure. Stapler division of the pancreatic parenchyma has already been found that is a simple, quick, and secure method of pancreatic stump closure[1,6,15]. The study by Bassi *et al*[16] is the only randomized controlled trial that compared the two techniques. They observed that using the stapler technique had better results in comparison with the suture closure (stapler 14% vs hand suture 33%). Takeuchi *et al*[1] described a statistically significant reduction in fistula rate after stapler closure, Fahy *et al*[9] described suture closure as a risk factor for pancreatic fistula, while Sheehan *et al*[2] found that the suture closure of the pancreatic remnant was superior compared with the stapler closure (25% *vs* 14% respectively). Finally, Kajiyama *et al*[15] and Bilimoria *et al*[7] found no differences between the two techniques. In our study, the authors' technical approach involved stapler and suture closure of the resected pancreatic parenchyma; in 45% of the patients the pancreatic parenchyma was closured using a linear stapler (GIA), while in 55% of the patients an absorbable monofilament 3-0 suture was used. We were unable to determine the advantage of one method of pancreatic remnant closure on the development of pancreatic fistula: onset of fistula was observed in 24% of patients in stapler group, and in 20% of patients in hand suture group.

Several studies have shown that fistula formation was not related to the main pancreatic duct ligation[3,17], while others reported the opposite[6]. We ligated and closed the main pancreatic duct with sutures in all patients after DP thinking that may be helpful in reducing possible pancreatic leaks. In almost all of them, we had no difficulty to find out the pancreatic duct. However, there was no significant difference according to the incidence of pancreatic fistula in our study in comparison with the literature studies[3,4,7-9].

Many authors state that the texture of the pancreatic parenchyma seems generally to be one of the most important risk factors responsible for the increased rate of pancreatic fistula[2,9]. The fibrotic pancreatic tissue is believed to be less likely to pancreatic leakage. In accordance with the reported studies, we observed that the patients with soft pancreatic tissue had higher incidence of pancreatic leakage compared with them who had fibrotic pancreatic parenchyma (44% *vs* 5%, $P = 0.006$).

We used postoperative prophylactic octreotide treatment in 53% of the patients and 12% of them developed a pancreatic leak, compared with 33% of patients who did not receive octreotide. However, the role of this treatment still remains unclear. Two randomized trials by Lowy *et al*[18] and Yeo *et al*[19] failed to identify a decrease in the pancreatic leakage in patients underwent pancreaticoduodenectomy, while Gouillat *et al*[20] demonstrated a decreased leak rate in a randomized trial of patients who underwent pancreaticoduodenectomy. Buchler *et al*[21] reported that the use of octreotide could prevent pancreatic fistula following pancreatic resection. They showed that the incidence of pancreatic fistula was 18% in the patients received perioperative octreotide treatment and 37% in patients received placebo after pancreatic resection. Suc *et al*[22] also described the advantage of using octreotide after pancreaticoduodenectomy.

The present report also highlights the importance of the primary disease in development of pancreatic fistula after DP: the patients underwent DP for pancreatic disease only had a higher incidence of pancreatic fistula compared with them who underwent DP for non-pancreatic malignancies. There is no doubt that it represents a quite strange observation because in patients with DP due to extrapancreatic malignancies the pancreatic tissue is generally softer than them who undergo DP for pancreatic diseases and we have no scientific explanation. However, new and larger studies are needed to determine if the extrapancreatic malignancies are associated with lower risk of pancreatic fistula after DP or not. Interestingly, there are no studies in the literature, at our knowledge, that examine the primary disease as significant risk factor

in the onset of pancreatic fistula. In published series, only the underlying pancreatic disease have examined as a responsible factor for the occurrence of pancreatic leakage[2,9]. This is the first study to show that primary (pancreatic and non-pancreatic) disease is a risk factor for postoperative morbidity after DP, especially for pancreatic leakage ($P = 0.04$).

In this study, postoperative comparison suggests that the patients underwent DP with splenectomy had a significantly lower incidence of postoperative pancreatic leakage compared with patients who underwent DP with spleen preserving. In contrast, Balzano *et al*[4] reported that their patients with spleen preservation had less pancreatic leakage compared to patients with splenectomy (20% *vs* 38%, $P = 0.15$), while Lillemoe *et al*[23] reported that the patients who underwent a DP with splenectomy had a similar complication rate (30% *vs* 29%) compared to patients who underwent spleen preserving DP, but with no specific focus on pancreatic leak.

Finally, we did not find a relation between the onset of pancreatic fistula and demographic factors (age, gender) nor with the technique of pancreatic closure (there has not been any correlation between pancreatic texture and the dissection technique used) and the additional procedures. In our series, fistula occurred similarly in patients who underwent pancreatic resection only and in patients who underwent one or more additional procedures.

In conclusion, pancreatic fistula after DP affects 22% of patients. None of the two techniques we used seemed useful to significantly reduce this incidence. Based on these findings, we support that the role that technique (either stapler or suture) of pancreatic stump closure plays in the development of pancreatic leak is unclear. Both techniques are regarded as simple, quick and secure although the fistula rate remains high. However, there is a clearly determined relationship between the primary pathology, the octreotide therapy, the texture of the pancreatic parenchyma, the concomitant splenectomy and the postoperative pancreatic fistula formation.

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