

ORIGINAL ARTICLE

PANCREATIC FISTULA AFTER PANCREATIC RESECTION: RISK AND MANAGEMENT

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Abstract

Aim of this study: Was to identify the risk factors and the outcome of management of pancreatic fistula after pancreatic resection.

Methods: This prospective study included 65 consecutive pancreaticoduodenectomy performed for patients with pancreatic or periampullary tumors. Pancreatico-jejunal anastomosis was done by duct-to-mucosa method in 57 patients and by dunking method in 8 patients. Postoperative evaluation included estimation of the drain output and its amylase content.

Results: The patients were 34 (52.3%) males and 31 (47.7%) females. Nine patients (13.8%) developed fistula. There was statistically significant association between the development of pancreatic fistula and small caliber of pancreatic duct <3mm, soft pancreas, plasma albumin < 3gm/dl and dunking anastomosis. Five patients recovered by conservative treatment alone. Three patients needed interventional radiology in addition to conservative treatment. Two patients died.

Conclusion: Many risk factors of pancreatic fistula were identified. The majority of pancreatic fistulae could be treated successfully by conservative treatment alone or with interventional radiology.

Keywords: Pancreaticojejunostomy, pancreatic duct caliber, interventional radiology.

INTRODUCTION

Progress in surgical techniques and perioperative management has substantially reduced the mortality rate of pancreatic surgery. Pancreaticoduodenectomy (PD) has been performed with an operative mortality of less than 5% in many large-volume centers. However, this operation is still associated with a high incidence of postoperative morbidity which may approach 50%.⁽¹⁻³⁾

Pancreatic fistula is the most important relevant complication, which can be responsible for approximately 80% of perioperative mortality after pancreatic resection. The incidence of pancreatic fistula varies from 5 to 25% in most series and many factors are involved as risk factors.(4,5)

The management of pancreatic fistula represents a real challenge. Sepsis and hemorrhage, caused by pancreatic fistula, are associated with mortality of 20 to 40%.⁽⁶⁾

The aim of this study was to identify the risk factors for the development of pancreatic fistula after pancreaticoduodenectomy as well as the outcome of its management.

PATIENTS AND METHODS

This prospective study included 65 consecutive

patients with malignant pancreatic tumors treated by pancreatico-duodenectomy. This was from March 2006 to August 2011. Nine of them (13.8%) developed pancreatic fistula. This study was approved by the Ethics Committee in Faculty of Medicine, Alexandria University.

Patients were subjected to full medical history, thorough clinical examination, laboratory investigations including liver function tests and tumor markers (CEA and CA 19-9), and abdominal imaging including ultrasonography, CT and cholangiography. ERCP was performed for 47 (72%) patients and MRCP for 32 (49.2%) patients; so both ERCP and MRCP were done for 14 (21.5%) patients. The diagnosis of pancreatic or periampullary tumors depended on tumor location in CT, detection of periampullary tumor by ERCP, MRI performed with MRCP, intraoperative location of the tumor and postoperative histopathology. Intraoperative assessment was done including the size of pancreatic duct, the consistency of the pancreas, the type of pancreatic anastomosis, the use of plastic stents for pancreatic anastomosis, blood loss and duration of operation. The pancreas was defined as soft or firm by palpation, by resistance during resection and by ability to hold sutures. The caliber of pancreatic duct was measured intraoperatively by a sterile ruler and was correlated with preoperative ultrasonographic measurement.

Pancreaticojejunostomy was done in all patients after PD. Duct-to-mucosa pancreatico-jejunostomy was the preferred technique.⁽⁷⁾ Prolene 5/0 with rounded needle was used for the duct-to-mucosa anastomosis. A short plastic stent was used according to the surgeon's preference. Dunking method⁽⁷⁾ was used for patients with small pancreatic duct and soft pancreas when there was technical difficulty to perform duct-tomucosa anastomosis.

Postoperative surveillance for pancreatic fistula included estimation of the amount of the drain output and its amylase content. The estimation of amylase content was done on the fourth day and was repeated when needed for follow up. Pancreatic fistula was diagnosed when the amylase content in the drain output exceeded 300U/L.^(1,7) Patients were also evaluated for any associated clinical findings including abdominal pain and distension with impaired bowel function, dyspnea, fever (>38°C), tachycardia and serum leukocytic count greater than 10,000 cells/mm3. Other more serious presentations can include intra-abdominal fluid collection (usually an abscess), haemorrhage from an eroded blood vessel.

The pancreatic fistulae were graded according to the system proposed by the International Study Group of Pancreatic Fistula (ISGPF)⁽⁸⁾ which classify pancreatic fistulae into three grades. Grade A fistulae which are asymptomatic with only elevated drain amylase and no suspicious collections. Grade B fistulae are

symptomatic; suspicious collections may be seen, but invasive treatment is not required. Grade C fistulae are clinically severe; the patients are frequently in critical condition with failed conservative treatment, and this grade includes any fistula requiring radiological or surgical intervention.⁽⁸⁾

The conservative treatment was used initially in all patients who developed pancreatic fistula. It consisted of NPO, octreotide (one ampoule every 8 hours), parenteral nutrition, parentral antibiotics, plasma transfusion. Interventional radiology was used by insertion of ultrasound-guided drains whenever there was a significant intra-abdominal collection.

Statistics: Data are presented, when appropriate, as median and percentage. The Fisher's exact and chi-squared tests were performed for univariate analyses of categorical values. Logistic regression was performed for multivariate model with P values and 95% confidence intervals estimated by the Wald method. A value of P \leq 0.05 was considered statistically significant. All data analyses were performed with the Statistical Package for the Social Sciences version 18 software (SPSS, Inc., Chicago, IL).

RESULTS

The studied patients were 34 (52.3%) males and 31 (47.7%) females. Their median age was 58 years (range 46-73 years). The clinical presentation included jaundice in all patients, dyspepsia in 51 (78.4%) patients, abdominal pain in 58 (89.2%) patients, weight loss in 32 (49.2%) patients and abdominal mass 17 (26.15%) patients.

Preoperative laboratory investigations revealed elevated serum bilirubin in 65 (100%) patients with a median of 11.9mg/dl. Median plasma albumin at presentation was 2.9gm/dl. (range:2.5-4.3mg/dl). Preoperative tumor markers, CA 19-9 and/or CEA, were elevated in 46 (70.7%) patients.

The tumors were in the head of pancreas in 57 (87.7%) patients and periampullary tumors in 8 (12.3%) patients.

Associated preoperative morbidities were present in 12 (18.4%) patients and included diabetes mellitus in 7 patients, hypertension in 3 patients, chronic obstructive pulmonary disease in one patient and liver cirrhosis in one patient.

Pancreaticojejunostomy was done by duct-to-mucosa method in 57 patients and by dunking method in 8 patients. The median intraoperative blood loss was 700ml (range: 500-950 ml), while the median operative time was 290 minutes (range: 255-340 minutes). The hospital stay ranged from 7 to 34 days with a median of 17 days. Nine (13.8%) patients developed pancreatic fistula. Other preoperative and operative data are shown in Tables 1,2. The amount of drain output in the

patients with fistula ranged from 260 to 700 ml/day with a median of 450ml/ day; whereas the median level of amylase content in the drain output was 760 U/L (range: 430-2200 U/L). Four patients had grade a pancreatic fistula. They were asymptomatic with just elevated level of amylase in the drain output. Two patients had grade B fistula with abdominal pain,

fever and intra-peritoneal collection that resolved by conservative treatment. Three patients had grade C fistulae. They presented with fever, abdominal pain, abdominal distension, and/or dyspnea. They all had an intra-abdominal collection that required percutaneous drainage achieved by interventional radiology.

		Patients with fistula (n=9)	Patients without fistula (n=56)	P-value	Risk of fistula	95% CI (lower – upper)
Age	<60 years	2	27	$x^{2}p = 0.145$	3.259	(0.622 – 17.080)
5	>60 years	7	29			(
Sex	Male	6	28	FEp = 0.480	2.00	(0.455 – 8.80)
	Female	3	28			
Serum	n bilirubin					
	< 15mg/dl	4	29	FEp = 0.733	1.343	(0.326 - 5.529)
	>15mg/dl	5	27			
Plasm	a albumin					
	<u><</u> 3gm/dl	6	12	FEp = 0.011*	7.333*	(1.595 – 33.726)
	> 3gm/dl	3	44	·		
Co-mo	orbidities					
	Present	3	9	FEp=0.349	2.61	(0.549-12.409)
	Absent	6	47			

FEp: p value for Fisher Exact test.

x²p: p value for Chi square test.

*: Statistically significant at $p \le 0.05$.

Table 2. Intra-operative data	a of patients with and without fistula
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	Patients with fistula (n=9)	Patients without fistula (n=56)	FEp-value	Risk of fistula	95% CI (lower – upper)
Pancreatic duct caliber			<0.001*	35.700*	(5.783 – 220.379)
<3mm	7	5			(******,
>3mm	2	51			
Consistency of pancreas			0.022*	7.389*	(1.393 – 39.194)
Soft	7	18			· · · · ·
Firm	2	38			
Method of anastomosis			0.049*	6.5*	(1.165-36.263)
Duct to mucosa	5	52			(
Dunking	4	4			
Trans-anastomotic stent			0.667	0.761	(0.137 – 4.223)
inserted	2	10			
not inserted	7	46			

FEp: p value for Fisher Exact test.

*: Statistically significant at $p \le 0.05$.

	В	Sig	OR	95% CI (Lower – upper)
Plasma albumin	-1.776	0.058	0.169	0.027 - 1.062
Pancreatic duct caliber	-1.045	0.030*	0.352*	0.137 - 0.903
Consistency of pancreas	1.140	0.287	3.128	0.384 - 25.497
Method of anastomosis	-0.799	0.562	0.450	0.030 - 6.688

Table 3. Multivariate logistic regression model (N = 65).

B: Coefficient of regression.

OR: Odd's ratio.

95% CI: 95% Confidence interval.

Additionally, intra-abdominal bleeding occurred in one patient. Two patients with Grade C fistula died. The cause of death was intra-abdominal bleeding in one patient and multi-organ failure secondary to sepsis in the second.

The other seven (77.8%) patients with pancreatic fistula were treated successfully by conservative treatment in addition to interventional radiology in one of them to insert ultrasound-guided drains.

The statistical comparison of the two groups of patients with and without fistula showed a significant p value for some factors Tables 1,2. According to univariate analysis, small caliber of pancreatic duct (\leq 3mm), soft pancreas, dunking anastomosis and low plasma albumin (\leq 3 g/dl) showed a statistically significant association with the development of pancreatic fistula. In the multivariate analysis, only the pancreatic duct caliber was statistically predictive Table 3.

DISCUSSION

Postoperative pancreatic fistula remains the most feared complication after pancreatico-duodenectomy. Its incidence ranges from 3% to 36% depending upon the definition used.(1,6,8-10) Several definitions of pancreatic fistula were considered in many studies. This resulted in much variability of reported incidence of pancreatic fistula according to the used definition.^(1,10-12)

Nowadays, there is a consensus that the pancreatic fistula is defined and graded according to the system proposed by the International Study Group of Pancreatic Fistula (ISGPF). The fistula is considered if there is any drain output with an amylase content more than 3 times the upper limit of the normal serum amylase (>300 IU/L) at postoperative day 3 or later. In addition, any complication of an intra-abdominal collection or abscess regardless of amylase content in the absence of an anastomotic leak is considered to be secondary to a pancreatic fistula.^(1,8,10)

In this study, 9 (13.8%) patients developed pancreatic fistula. According to ISGPF classification, four fistulae

were grade A (44.4%), two were grade B (22.2%) and three were grade C (33.3 %).

The risk of fistula formation has been reported to be affected by the type of pancreatic anastomosis and the surgical technique. Two methods of pancreaticojejunostomy were used in the present study; duct to mucosa in 57 patients and dunking in 8 patients. Dunking method was more associated with the development of fistula than duct to mucosa anastomosis. Using a univariate analysis, the difference was statistically significant. However, in a multivariate analysis the difference was not statistically significant. Many studies showed lower rates of fistulae with isolated defunctioned duct-to-mucosa pancreaticojejunostomy.^(3,13) End to side pancreatico-jejunostomy had lower rate of fistulae (11.9%) than invaginating end to end anastomosis (50%).⁽¹⁴⁾ A meta-analysis study that pancreatogastrectomy showed and pancreatojejunostomy had similar pancreatic fistula rates and morbidity rates. However, pancreatico-jejunostomy is still the most common type of anastomosis done.⁽¹⁵⁾

The incidence of pancreatic fistula decreases with tension-free anastomosis and fine sutures.⁽³⁾ The surgeon's experience with one or other technique of pancreatic anastomosis appears more important than the technique itself.⁽²⁾

A pancreatic duct stent for internal or external drainage has been thought to reduce the pancreatic leakage rate after pancreatoduodenectomies particularly in patients with a small pancreatic duct and a soft pancreas. A stent might help drain the pancreatic secretion juice from the anastomosis, and allow a more precise placement of sutures, thus protecting the pancreatic duct from injury and reducing fistula rate and preventing accidental suturing of both anterior and posterior walls. However, the theoretical advantage of stenting has never been confirmed in randomized trials and other groups have not observed similar benefits.⁽¹⁶⁻¹⁹⁾ In our study, short trans-anastomotic stents were used in 12 patients with no statistically significant association with development of pancreatic fistula. Many risk factors associated with the increased incidence of pancreatic fistula have been reported in the literature. These risk factors include soft pancreatic texture, small diameter of pancreatic duct, decrease pancreatic vascularity, good volume of pancreatic juice output, old age, male gender, decreased plasma albumin, markedly elevated bilirubin, obesity, comorbid illness, long operative time, intraoperative blood loss > one liter, invaginated type of pancreatic anastomosis and pancreatic duct occlusion.(3,6,9,20-23) The risk factors identified in the present study were small caliber of pancreatic duct ≤ 3 mm, soft pancreas, dunking anastomosis and plasma albumin ≤ 3 gm/dl.

Currently, the management of a pancreatic fistula after pancreatico-duodenectomy is not standardized. Most studies reported that the majority of fistulae (90%) can be managed conservatively with antibiotics, supplemental nutrition, somatostatin analogues and adequate drainage.(6,10) Grade A pancreatic fistula is the most common grade and has no major clinical impact. Grade B fistula may be associated with abdominal pain, fever, leukocytosis. Grade A and B fistulae are managed by conservative treatment in addition to gradual removal of the drains that were placed intraoperatively. CT or ultrasound-guided drains are required when there is grade C fistula with abdominal collection. Grade C fistula is the most severe, with high mortality rate. It usually presents with abscess, peritonitis, sepsis or hemorrhage. Treatment of this life-threatening condition can be conventional with image-guided or operative drainage, or more aggressive with completion pancreatosplenectomy for patients not improving with measures. However, conventional completion pancreatectomy has high perioperative mortality ranging between 75 to 100%.(1,10)

In this study, seven patients (77.8% of fistulae) were managed successfully by conservative treatment; one of them required ultrasound-guided drainage. Two patients died giving a mortality of 22.2% for patients who developed fistula.

In conclusion pancreatic anastomotic leakage is a serious complication after PD with a significant mortality. The risk factors of pancreatic fistula included small caliber of pancreatic duct \leq 3mm, soft pancreas, dunking anastomosis and plasma albumin \leq 3gm/dl. The majority of pancreatic fistulae (77.8%) could be treated successfully by conservative treatment alone or with interventional radiology.

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