

Risk factors associated with pancreatic fistula after distal pancreatectomy

Amin Makni, Wael Rebai, Amin Daghfouss, Sofiene Ayadi, Fadhel Fterich, Faouzi Chebbi, Rachid Ksantini, Mohamed Jouini, Montassar Kacem, Zoubeir Ben Safta

Department of digestive surgery 'A', La Rabta hospital, Tunisia
Tunis Medical School - Tunis El Manar University

A. Makni, W. Rebai, A. Daghfouss, S. Ayadi, F. Fterich, F. Chebbi, R. Ksantini, M. Jouini, M. Kacem, Z. Ben Safta

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Facteurs de risque de fistule pancréatique après pancréatectomies gauches

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RÉSUMÉ

Prérequis : La fistule pancréatique demeure la principale cause de morbidité après résection pancréatique.

But: Identifier les facteurs de risque de survenue de fistule pancréatique après pancréatectomie gauche.

Méthodes: Trente cinq patients ont subi une pancréatectomie gauche durant une période de 10 ans (2000-2009). Nous avons recueilli les caractéristiques épidémiologiques et les données opératoires. Nous avons décrit la morbidité et la mortalité opératoire. Neuf facteurs de risque de survenue de fistule pancréatique ont été étudiés.

Résultats: La pancréatectomie gauche a été réalisée aussi bien pour une pathologie pancréatique (n=23; 66 %) que pour une pathologie extra-pancréatique (n = 12; 34 %). La morbidité postopératoire était de 43 % avec une mortalité nulle. Aucune reprise chirurgicale n'a été indiquée. Une fistule pancréatique a été diagnostiquée chez 11 patients (31 %). En étude univariée, aucun de ces facteurs de risque suivant n'a été associé à une variation significative du taux de fistule pancréatique: la pathologie causale, la prévention par l'Octréotide, la splénectomie, le geste chirurgical associé, le saignement peropératoire et la texture du parenchyme pancréatique. Nous avons observé une différence statistiquement significative en rapport avec le sexe; 47 % des femmes contre 17 % des hommes ont présenté une fistule pancréatique (p = 0,05). La relation entre les artifices techniques utilisés pour le traitement du moignon pancréatique après pancréatectomie gauche et la survenue de fistule pancréatique reste à déterminer vu le faible nombre de patient chez qui nous avons utilisé une pince coupante linéaire à auto-suture mécanique.

Conclusion: Le taux de fistule pancréatique après pancréatectomie gauche est de 31 %. Le sexe féminin a été identifié comme étant un facteur de risque de survenue de fistule pancréatique après pancréatectomie gauche. Le rôle incriminé à l'usage d'une pince mécanique pour le traitement du moignon pancréatique requiert un nombre plus important de patient pour pouvoir conclure. L'index de masse corporelle n'a pas été étudié dans notre série.

SUMMARY

Background: Pancreatic leak (PL) remains a major cause of postoperative morbidity in patients undergoing pancreatic resection.

Aim: To identify risk factors related to pancreatic fistula in patients undergoing distal pancreatectomy (DP).

Methods: 35 patients underwent DP during a 10-year period (2000-2009). Informations regarding diagnosis, operative details, and perioperative morbidity and mortality were collected. Nine risk factors were examined.

Results: Indications for DP included primary pancreatic disease (n=23; 66 %) and non-pancreatic disease (n = 12; 34 %). Postoperative morbidity rate was 43 % and none patient died. No patients required a reoperation. Pancreatic fistula was occurred in 11 patients (31 %). On univariate analysis, incidence of pancreatic fistula rate was not significantly associated with these risk factors: pathology, use of prophylactic octreotide therapy, concomitant splenectomy, additional procedures, intra operative bleeding and texture of pancreatic parenchyma. We observed significant statistical difference between male and female, 47 % of females experienced a pancreatic fistula, while 17 % males developed a pancreatic leakage (p=0.05). The role of the technique of pancreatic stump closure in the development of pancreatic leak remains unclear because of the few number of patients on who we used stapler.

Conclusion: The rate of pancreatic fistula after left pancreatectomy is 31 %. The female was identified as a risk factor for occurrence of pancreatic fistula after left pancreatectomy. The role implicated in the use of a mechanical claw for the treatment of pancreatic stump requires a larger number of patients to conclude. The body mass index has not been studied in our series.

Mots-clés

Pancréatectomie- fistule pancréatique- pancréatectomie gauche

Key- words

Pancreatectomy- pancreatic- fistula- left pancreatectomy

Distal pancreatectomy (DP) is defined as the resection of pancreatic tissue to the left of the superior mesenteric vessels. 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% [1]. Pancreatic leakage often leads to further complications, such as fluid collections or intra-abdominal abscesses, wound infections, respiratory complications, and sepsis [1]. The risk factors in the development of pancreatic fistula are also unclear. Malignancy, trauma, patient's age, concomitant splenectomy, additional procedures, the method of pancreatic stump closure or obesity are implicated as potentially important [2, 3]. The purpose of this study was to determine possible risk factors that may be associated with the onset of pancreatic fistula after DP.

PATIENTS AND METHODS

A retrospective review of 35 patients who underwent DP from January 2000 to December 2009 at the Department of Digestive Surgery 'A', La Rabta University Hospital of Tunis, was conducted. Patient's age, sex, indications for surgery, concomitant splenectomy, additional procedures, methods of pancreatic stump closure, and postoperative complications especially pancreatic leaks, mortality, and duration of postoperative hospital stay were recorded. Operative details also included intra operative bleeding and the texture of pancreatic parenchyma. No patient was excluded from this study.

The indications for DP included either primary pancreatic diseases or non-pancreatic diseases. All the operations were performed by the same surgical team. Division of the pancreatic parenchyma was done by knife or stapler (TA 60), while the pancreatic remnant was either closed by a linear stapler or by hand running absorbable monofilament 4-0 sutures. Two open drains were positioned near the transected pancreas. We used prophylactic octreotide in the last 11 patients (34 %), postoperatively for seven days, and in cases with fistula the octreotide was prolonged until recovery. The dose of octreotide was 100 μ g three times a day. Postoperative mortality and morbidity were registered for 30 days or during the total hospitalisation time, if longer. Concerning postoperative pancreatic leaks, we have used the definition, now known as the International Study Group on Pancreatic Fistula (ISGPF) definition [4]. The definition was intended to standardize the reporting of postoperative PF. The essential component of an anastomotic leak was the high amylase content (> 3 times the upper normal serum value), of the drain fluid (of any measurable volume), at any time on or after the 3rd postoperative day. The following nine risk factors were analysed: age (patients older or younger than the age of 65 years), gender, pancreatic disease or non-pancreatic malignancy, technique of pancreatic stump closure, splenic preservation, texture of the pancreatic parenchyma (soft or

fibrotic tissue), additional procedures, postoperative use of octreotide and intra operative bleeding. The texture of the pancreatic parenchyma was adequately defined by histopathology examination.

Statistical analysis

All data were reported as the median and range values. The data were analyzed by means of SPSS 9.00 statistical package for Windows. Mann-Whitney U test and Chi-square test (Fisher exact test in the case of small numbers) was used for group comparison and Student's t test to analyze normally distributed quantitative data. $P < 0.05$ was considered statistically significant. First of all, the univariate analysis was done. Next, the multivariate analysis was performed using a logistic regression model for multiple data expressed in odds ratios (ORs). To test the independence of the risk factors, the significant variables ($p < 0.2$) in the univariate analysis were entered into a multivariate logistic regression model with likelihood ratio forward selection with a criterion of $p < 0.05$.

RESULTS

All patients underwent DP for elective benign or malignant, pancreatic or non-pancreatic diseases. There were 18 males (51%) and 17 females (49%). The patient's age ranged from 19 to 75 years (median age: 50 years). The indications for surgery included 23 patients (66%) with pancreatic disease and 12 patients (34 %) with non-pancreatic disease. The indications of DP are listed in Table 1.

Table 1 : Indications for Distal Pancreatectomy

Indications	Number of patients (Rate %)
Benign	18 (51)
Pseudocyst	1 (3)
Mucinous cystadenoma	5 (14)
IPMT	1 (3)
Chronic pancreatitis	2 (6)
Trauma	1 (3)
Serous cystadenoma	2 (6)
Endocrine tumor	4 (11)
Teratoma	1 (3)
Splenic artery aneurysm	1 (3)
Malignant	17 (49)
Endocrine tumor	2 (6)
Ductal adenocarcinoma	5 (14)
Gastric adenocarcinoma	10 (29)

IPMT, intraductal papillary mucinous tumor.

Thirty patients (85 %) underwent DP with splenectomy. A spleen preserving DP was performed in 5 patients (14 %), they all had benign or borderline diseases. The overall number of additional procedures was 14 (40 %): One of these patients (7

(%) had primary pancreatic malignancy infiltrating surrounding organs and 11 patients (79 %) had non-pancreatic malignancy infiltrated pancreas. The transfusion of more than two units of packed red blood cell was necessary in seven cases (20 %). The patient's demographics, operative and technical factors are summarized in Table 2.

Table 2 : Patients' demographics, operative and technical factors

	Number of patients (Rate %)
Sex	
Male	18 (51)
Female	17 (49)
Operations	
DP + splenectomy	30 (86)
Spleen preserving DP	5 (14)
DP + additional procedure (Splenectomy excluded)	14 (40)
Additional procedures	
Gastrectomy	11 (31)
Colon resection	1 (3)
Thoracotomy of hemostasis	1 (3)
Gastroenteroanastomosis + truncular vagotomy	1 (3)
Closure of pancreatic stump	
Suture	32 (91)
Stapler	2 (6)
Pancreaticojejunostomy	1 (3)

The median postoperative length of hospital stay, in patients without fistula, was 11 days (Range values; 6 - 25 days); while in patients with pancreatic fistula the median hospitalization was extended of 21 days (Range values; 7 - 68 days) ($p=0.001$). No death occurred, while the morbidity rate was 43 % ($n = 15$). Eleven patients (31 %) developed a pancreatic fistula. No one required a second operation. Patients with intra-abdominal abscess or fluid collection were treated by percutaneous drainage in four cases (11 %). Postoperative variables are showed in Table 3.

Table 3 : Post operative results

	Number of patient (Rate %)
Death	0 (0)
Reoperation	0 (0)
Complications	
No	20 (57)
Yes	15 (43)
Pancreatic fistula	11 (31)
Others	
Chylous fistula	1 (3)
Intra-abdominal hemorrhage	0 (0)
Intra-abdominal abscess	5 (14)
Pulmonary	2 (6)

Univariate analysis

Pancreatic fistula was significantly more common in patients who underwent DP with technique of pancreatic stump closure using stapler in two cases (100%), compared with 9 (27 %) of 32 patients who underwent DP with suture closure of pancreatic stump ($p = 0.03$). However, the powerless of the Fisher's exact test is due to the slight effective (2 cases). In one case (3%), we have performed a pancreatico-jejunostomy because of the diameter of pancreatic duct (more than 1 cm). We observed significant statistical difference between male and female, 8 (47 %) of 17 females experienced a pancreatic fistula, while 3 (17 %) of 18 males developed a pancreatic leakage ($p = 0.05$). Seven among nine studied factors such as age, pancreatic disease or non-pancreatic disease, splenic preservation, texture of the pancreatic parenchyma, additional procedures, postoperative use of octreotide and intra operative bleeding were not significantly associated with pancreatic fistula formation. The incidence of pancreatic fistula after DP according to the nine examined risk factors is summarized in Table 4.

Multivariate analysis

On multivariate analysis, in addition to these 2 factors, an additional procedure, was predictive of a clinically significant PF. Using stapler for closing a pancreatic stump ($p < 0.001$), female ($p = 0.002$) and additional procedures ($p=0.027$) were independent risk factors for developing a PF. In this study, a trend towards significance was found with concomitant splenectomy ($p=0.055$) and a post operative use of octreotide ($p=0.055$). Multivariate analyses of factors associated with post operative pancreatic fistula are summarized in Table 5.

Table 5 : Multivariate analyses of factors associated with post operative pancreatic fistula

Factor	Odds ratio (CI*)	p value
		0.002
Female	1.37 (0.9-10.6)	< 0.001
Pancreatic stump closure using stapler	3.46 (2.10-6.40)	0.027
Additional procedures	4 (0.78-20.3)	0.055
Concomitant splenectomy	8.46 (0.5-9.8)	0.055
Use of Octreotide	4.15 (0.06-7.11)	

* CI: Confident interval at 95%

DISCUSSION

Our findings identify the importance of one risk factor in the development of pancreatic fistula: the technique of pancreatic stump closure using stapler was correlated with a statistically significant reduction in the rate of postoperative pancreatic leakage. Pancreatic fistula was significantly more common in females and in patients on who we performed a concomitant splenectomy. No significant differences were found regarding the onset of pancreatic fistula for the rest of the examined factors such as age, additional procedures, fibrotic pancreatic parenchyma, non pancreatic disease, duration of operation, intra

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

	Patients n (Rate %)	Fistula n (Rate %)		<i>p</i> value	Odds ratio (CI**)
		No	Yes		
	35 (100)	24 (69)	11 (31)		
Sex					
Male	18 (51)	15 (83)	3 (17)	0.05	0.22 (0.04- 1.07)
Female	17 (49)	9 (53)	8 (47)		
Age (Year)					
> or = 65	9 (26)	7 (78)	2 (22)	0.49	1.85 (0.31-10.8)
< 65	26 (74)	17 (65)	9 (35)		
Pancreatic stump closure					
Suture	32 (91)	23 (72)	9 (28)	0.03*	3.66 (2.10-6.40)
Stapler	2 (6)	0 (0)	2 (100)		
Pathology					
Pancreatic disease	23 (66)	17 (74)	6 (17)	0.34	0.49 (0.11-2.16)
Non-pancreatic disease	12 (34)	7 (58)	5 (42)		
Octreotide					
Yes	24 (69)	15 (63)	9 (38)	0.25	0.37 (0.06-2.11)
No	11 (31)	9 (82)	2 (18)		
Texture of pancreatic parenchyma					
Soft	29 (83)	19 (66)	10 (34)	0.39	0.38 (0.03- 3.71)
Fibrotic	6 (17)	5 (83)	1 (17)		
Concomitant splenectomy					
Yes	30 (86)	19 (63)	11 (37)	0.10	0.63 (0.48-0.83)
No	5 (14)	5 (100)	0 (0)		
Procedures					
Pancreatic resection only	21 (60)	16 (72)	5 (24)	0.20	2.40 (0.55- 10.32)
Additional procedures	14 (40)	8 (57)	6 (43)		
Transfusion > or = 2 units PRBC					
Yes	7 (20)	4 (57)	3 (43)	0.46	1.87 (0.34-10.33)
No	28 (80)	20 (71)	8 (28)		

operative bleeding and postoperative prophylactic octreotide therapy.

Mortality and morbidity after DP have significantly decreased the last decades [5]. In this study, we support that DP can be performed without mortality (0 %) [6-8], while the incidence of pancreatic fistula, the most common postoperative complication, was 31 %. The same results are reported by most of authors' conclusions [2, 3, 9, 10, 11].

Pancreatic fistula complicates 3% to 26% of DP [5, 10, 7] This wide variability of the PF rate following DP is probably

explained by the variability of the definition of PF in the literature. In our study, we have used the definition reported by Gouillat C et al [4]. Management of PF after DP is not fully standardized. In the present serie, conservative management was applied in all patients, including maintenance of intra operatively placed drains, additional per cutaneous drains when necessary and parenteral nutrition.

In order to reduce postoperative complications, especially pancreatic fistula, some surgical procedures for treating the resected pancreatic surface after DP has been proposed: hand-

sewn suture [6, 12], stapler [1, 6, 11, 12], a combination of stapler and suture [6, 11, 12], fibrin-glue sealing [13, 14], and prolamine injection [15]. The study by Bassi et al [16] is the only randomized controlled trial that compared stapler and suture closure. 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] and Fahy et al [17] found the same results. For Kajiyama *et al* [18] and Bilimoria et al [11], there are no differences between the two techniques described. However Sheehan et al [6] as well as our study found that the suture closure of the pancreatic remnant was superior compared with the stapler closure (25% vs 14% respectively). 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 [6, 17]. The fibrotic pancreatic tissue is believed to be less likely to pancreatic leakage. In opposition with the reported studies, we don't observed that the patients with soft pancreatic tissue had higher incidence of pancreatic leakage compared with them who had fibrotic pancreatic parenchyma (35 % vs 17 %, $P = 0.392$).

The role of prophylactic octreotide remains unclear. Two randomized trials by Lowy et al [19] and Yeo et al [20] failed to identify a decrease in the pancreatic leakage in patients undergoing pancreaticoduodenectomy, while Gouillat et al [21] demonstrated a decreased leak rate in a randomized trial of patients who underwent this procedure. Buchler et al [22] reported that the use of octreotide could prevent pancreatic fistula following pancreatic resection. We used postoperative prophylactic octreotide treatment in 31 % of the 35 patients and 44 % of them developed a pancreatic leak, compared with 22 % of patients who did not receive octreotide ($P = 0.18$).

The present report showed that there are no differences in development of pancreatic fistula when we compare patients

who underwent DP for pancreatic disease only and those who underwent DP for non-pancreatic malignancies. The only study is reported by Ridolfini et al [23]. It shows that primary (pancreatic and non-pancreatic) disease is a risk factor for pancreatic leakage ($P = 0.04$).

This study suggests that patients who underwent spleen preservation had less pancreatic leakage compared to patients with splenectomy, on multivariate analysis. Balzano et al [3] found similar results (20% vs 38%, $P = 0.15$). However, Lillemoe et al [10] reported that DP with splenectomy had a similar incidence of postoperative pancreatic leakage compared with patients who underwent DP with spleen preservation, while Ridolfini et al [23] reported that the patients who underwent a DP with splenectomy had less pancreatic leakage. Some other factors that may significantly increased the risk of PF: pancreatic transection at the body level (vs at the neck), absence of elective ligation of the main pancreatic duct and obesity need new and larger studies to determine if they are risk factors associated with PF after DP. In our study we didn't analyse these data. However, obesity may be correlated with gender. In fact, females was significantly increased the risk of PF.

CONCLUSION

Pancreatic fistula after DP affects 31 % of patients. Hand-sewn suture of pancreatic stump and splenic preservation reduce the incidence of pancreatic fistula. Nevertheless, the role that technique 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 not a relationship between the primary pathology, the octreotide therapy, the texture of the pancreatic parenchyma the postoperative pancreatic fistula formation.

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