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RISK FACTORS OF PANCREATIC FISTULA FOLLOWING PANCREATODUODENECTOMY

Sahakyan M.A.[1,2] *, Stepanyan S.A.[1], Gabrielyan A.M.[3], Petrosyan H.P.[3], Akunts A.R.[4], Sahakyan A.M.[1,3]

[1] Department of Surgery N1, Yerevan State Medical University, Yerevan, Armenia
[2] Interventional Centre, Oslo University Hospital – Rikshospitalet, Oslo, Norway
[3] Department of General and Abdominal Surgery, "Artmed" Medical Rehabilitation Centre, Yerevan, Armenia
[4] Department of Surgery, "Kanaker-Zeytun" Medical Centre, Yerevan, Armenia

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Abstract

Pancreatoduodenectomy is the main curative option for patients with periampullary malignancies. At the same time, the rate of postoperative complications remains high, ranging from 30 to 40%. Pancreatic fistula is the most common complication after pancreatoduodenectomy, leading to an increase in severe postoperative morbidity, mortality and prolonged length of hospital stay. Besides that, pancreatic fistula results in an increase in hospital costs. The present study aimed to analyze the perioperative outcomes in patients undergoing pancreatoduodenectomy in order to identify the specific risk factors for pancreatic fistula after surgery.

A total number of 79 patients consecutively underwent pancreatoduodenectomy for periampullary benign and malignant lesions from 2000 to 2014 in leading hospitals of Yerevan city.

In all, 21 (26.6%) patients were postoperatively diagnosed with pancreatic fistula, among of which clinically relevant pancreatic fistula (grade B and C) was developed in twelve (15.2%). Patients with and without clinically relevant pancreatic fistula were comparable in terms of pre- and intraoperative characteristics, except of pancreatic duct stenting. The latter was more often in those who were eventually diagnosed with clinically relevant pancreatic fistula (33% vs. 9%, p=0.04). The rates of postoperative complications, mortality and reoperations were significantly higher in patients with clinically relevant pancreatic fistula (p=0.001, 0.01 and 0.001, respectively). Accordingly, median length of hospital stay was also longer in this group 22 vs. 12 days, (p=0.001). According to the univariate analysis, the estimated intraoperative blood loss greater than 500ml, preoperative diabetes mellitus and pancreatic duct stenting during surgery had predictive value for the development of clinically relevant pancreatic fistula. Multivariate regression analysis estimated intraoperative blood loss greater than 500ml as the only independent risk factor for the development of clinically relevant pancreatic fistula (OR– 5.08; 95% CI–1.17-21.98).

Surgeons' experience can be one of the decisive factors affecting on the decrease of intraoperative blood loss during pancreatoduodenectomy. Hence, it is presumed that growing experience in implementation of these procedures will let to reduce the development rate of pancreatic fistula and improve short-term results after pancreatoduodenectomy in patients with periampullary malignancies.

Keywords: *pancreatoduodenectomy, pancreatic fistula, morbidity, mortality, blood loss.*

Introduction

Pancreatoduodenectomy is the main curative option for patients with periampullary malignancies. It is also applied for several benign periampullary lesions, requiring surgery.

Historically pancreatoduodenectomy has been a complex procedure leading to high rates of postoperative complications and mortality. However, recent advances in diagnostics of tumors, accurate preoperative planning, surgical technique and perioperative management of these patients enabled to significantly decrease postoperative mortality, which currently does not exceed 5% in high-volume centers. At the same time, in spite of the low postoperative mortality, the rate of postoperative complications remains high, ranging from 35 to 40% [*House M et al., 2008; Hashimoto D et al., 2014*].

Address for Correspondence:
Interventional Centre, Oslo University Hospital – Rikshospitalet
P.O. Box 4950 Nydalen, N-0424, Oslo, Norway
Tel.: (+47 486 63 546)
E-mail: sahakyan.mushegh@gmail.com

Pancreaticojejunostomy represents the Achilles heel of pancreatoduodenectomy. Relatively high incidence of anastomotic leakage from pancreaticojejunostomy, mainly due to a fragile pancreatic tissue, results in development of postoperative pancreatic fistula. The latter is a leading cause of complications after pancreatoduodenectomy and, according to the literature, occurs in up to 30% of cases. Pancreatic fistula also leads to severe postoperative complications, such as intraabdominal abscess, peritonitis and arrosive bleeding from major regional vessels. These complications usually require reoperation. As a result, pancreatic fistula significantly hampers patient recovery, increasing postoperative length of stay and hospital costs [*Bassi C et al., 2005b; Topal B et al., 2007; Ramacciato G et al., 2011; Hashimoto D et al., 2014*]. Thereby, the prevention of pancreatic fistula is one of the main objectives of pancreatic surgery.

Although various preoperative and intraoperative factors have been distinguished as potential triggers for the development of pancreatic fistula after pancreatoduodenectomy, suggested technical approaches with regards to pancreatic anastomosis, as well as medicamental prophylaxis of the activated exocrine pancreatic secretion have not resulted in improved outcomes following surgery. As a result, the rate of pancreatic fistula up to 25% is nowadays considered acceptable by experienced pancreatic surgeons [*Ramacciato G et al., 2011*].

The definition and classification of pancreatic fistula was considered as another major issue in pancreatic surgery over the decades. The lack of uniform definition and grading system for postoperative pancreatic fistula led to an explicit discrepancy between the results from surgical centers, reporting on incidence of pancreatic fistula following pancreatoduodenectomy. Finally, this issue was addressed in a consensus study from Bassi C and co-authors (2005), where the authors established both definition and severity grades for pancreatic fistula after pancreatic resections.

Current grading system classifies pancreatic fistula into three different groups as follows [*Bassi C et al., 2005a; Pratt W et al., 2007*]:

1. Grade A – transient or asymptomatic, have no clinical symptoms and impact on normal postoperative course. Abdominal drains are removed within 3 weeks after surgery.
2. Grade B – symptomatic, associated with fever, rigor, ailment, abdominal pain. Antibiotic therapy and/or percutaneous drainage are indicated to control and prevent the exacerbation of fistula. Abdominal drains are frequently required more than 3 weeks for the management.
3. Grade C – always result in serious complications (sepsis, organ failure, etc.), including lethal outcome. Relaparotomy is indicated in all patients.

According to the clinical classification by the International Study Group on Pancreatic Fistula (ISGPF) [*Bassi C et al., 2005a*], two major types of pancreatic fistula can be distinguished: transient or asymptomatic (grade A) and clinically relevant (grade B and C) [*Pratt W et al., 2007; Kim W et al., 2011*]. The latter is the main cause of postoperative mortality after pancreatoduodenectomy, defined as any death that occurred within 100 days, following surgery [*Strasberg S et al., 2009*].

In spite of uniform reports on pancreatic fistula from authors using the grading system from ISGPF, the reasons behind the development of this specific complication still remains unclear. Hence, taking into account the significance of clinically relevant pancreatic fistula in postoperative management of patients undergoing pancreatoduodenectomy, the identification of risk factors for pancreatic fistula is of great value and represents the first step towards the prevention of this hazard.

The aim of present study is the assessment of intraoperative parameters in patients with and without clinically relevant pancreatic fistulas after pancreatoduodenectomy and the determination of potential risk factors of their development.

MATERIALS AND METHODS

A total number of 79 patients consecutively underwent pancreatoduodenectomy for periampullary benign and malignant lesions from 2000 to 2014 at National Oncology Center after V.A. Fanarjyan (2000-2003), “Surb Nerses Astvatsamayr” Medical Center (2003-2004), “Kanaker-Zeytun” Medical Center (2004-2008), “Armenia” Republican Medical Centre (2005-2014.) and “Artmed” Medical Rehabilitation Center (2009-2014).

The amylase values in the serum and abdominal drainage fluid were measured in all patients from the first postoperative days. Abdominal drains were removed when the output was minimal and the amylase level was ≤100 *IU/L*. Pancreatic fistula was defined by the criteria of International Study Group on Pancreatic Fistula, as any measur-

able drainage from an operatively placed drain on or after 3 postoperative days, with an amylase content greater than 3 times upper limit of normal serum amylase level (>300 *IU/L*).

Patients, comprised in the study, were divided into two groups. The main group was consisted of patients with relevant pancreatic fistula (grade B and C), and the control group included the other patients including those with A grade fistula because of the absence of clinical aspects.

A comparative analysis of the outcomes between the groups was carried out. Categorical variables are presented as numbers and percentages, whereas continuous variables are expressed as median (range) or mean (interquartile range) values, depending on variable's distribution pattern. The analysis of normally distributed continuous variables was conducted using Student two-sample t-test, while the Mann-Whitney U test was applied for not normally distributed data. Chi-square or Fisher's exact test were used for the comparison of categorical outcomes. When the association probability was less than 0.05, the p-values were considered statistically significant. A logistic regression analysis was applied to identify the prognostic factors for pancreatic fistula. Parameters that were significant on univariate analysis ($p<0.1$) were included in the multivariable model in order to identify the independent risk factors for pancreatic fistula. On multivariate analysis the statistical significance was defined as $p<0.05$. The whole statistical analysis was performed using SPSS software (version 16.0).

RESULTS

From the entire cohort of 79 cases with pancreatoduodenectomy, 21 (26.6%) developed pancreatic fistula after surgery. Twelve out of 21 suffered from clinically relevant pancreatic fistula (Table 1).

TABLE 1.

Rate and severity of pancreatic fistula after pancreatoduodenectomy in total group of patients (n=79)

Grade	Number (%)
A	9 (11.4%)
B	8 (10.1%)
C	4 (5.1%)
Total number of cases	21 (26.6%)

The summary of perioperative outcomes in two groups is presented in Table 2. No significant differences were observed between the groups in terms of demographics, preoperative data, number of pylorus-preserving procedures and pancreatojejunostomy technique, even though intraoperative pancreatic duct stenting was more frequent in pancreatic fistula group (p=0.04). The latter had also higher rate of estimated blood loss and longer operating time. However, the difference was not statistically significant (p=0.058 and 0.072, respectively). The incidence of relaparotomy, as well as the rates of postoperative morbidity and mortality were expectedly higher in pancreatic fistula group (p=0.001, 0.001, 0.01, respectively). As a result, postoperative hospital stay also was longer in this group (p=0.001).

The results of the univariate analysis of predictors for clinically relevant pancreatic fistula are presented in Table 3. Preoperative diabetes mellitus was a significant predictor for pancreatic fistula (OR–6.77; 95% CI–0.84-54.3), estimated blood loss greater than 500*ml* during pancreatoduodenectomy (OR–5.04; 95% CI–1.24-20.38) and intraoperative stenting of the pancreatic duct (OR–5.08; 95% CI–1.17-21.98) were associated with development of pancreatic fistula after surgery.

The outcomes of the multivariate analysis are demonstrated in Table 4. Estimated blood loss greater than 500*ml* was the only independent predictor for clinically relevant pancreatic fistula after pancreatoduodenectomy (OR– 6.31; 95% CI–1.1-35.9).

DISCUSSION

The development of pancreatic fistula is a common problem in pancreatic surgery. The results of the present study confirm significant mortality (p=0.01) and morbidity in patients with clinically relevant pancreatic fistula, that also leads to prolonged hospital stay (p=0.001) after pancreatoduodenectomy.

The definition and proposed grading system by the International Study Group on Pancreatic Fistula [*Bassi C et al., 2005a; Pratt W et al., 2007*] enabled more thorough analysis of predictive factors and mechanisms responsible for the development of pancreatic fistula. Both intra- and postoperative parameters have been considered as potential predictors of pancreatic fistula [*House M et al., 2008; Pratt W et al., 2008; Ramacciato G et al., 2011; Cloyd J et al., 2014; El Nakeeb A et al., 2014*

TABLE 2.

Comparative analysis of perioperative outcomes in patients with and without pancreatic fistula

Variable	Control group (n=67)	Main group (n=12)	p
Age, years	58.9 (9.8)	58.6 (11.8)	0.92*
Gender, n (%)			0.2
Female	30 (44.8%)	3 (25%)	
Male	37 (55.2%)	9 (75%)	
Body mass index *kg/m²*	25.3 (17.8-41.7)	27.5 (24.7-35.2)	0.34**
Physical status classification system by *American Society of Anesthesiologists.*, n (%)			0.59
II	20 (29.9%)	2 (16.7%)	
III	38 (56.7%)	9 (75,0%)	
IV	9 (13.4%)	1 (8.3%)	
Patients with major comorbidities, n (%)	46 (68.6%)	7 (58.3%)	0.49
Number of major comorbidities	2 (1-4)	2 (1-3)	0.69**
Diabetes mellitus, n (%)	2 (3.2%)	2 (18.2%)	0.1
Primary diagnosis			0.511
Pancreatic cancer, n (%)	16 (23.9%)	3 (25%)	
Carcinoma of the ampulla of Vater, n (%)	31 (46.3%)	7 (58.3%)	
Other, n (%)	20 (29.8%)	2 (16.7%)	
Preoperative weight loss			0.38
< 6*kg, n (%)*	15 (22.4%)	3 (25%)	
6-10*kg, n (%)*	20 (29.8%)	6 (50%)	
> 10*kg, n (%)*	8 (11.9%)	0 (0%)	
Jaundice, n (%)	40 (63.5%)	8 (72.7%)	0.73
Preoperative interventions, n (%)	9 (14.3%)	2 (18.2%)	0.66
Preoperative serum bilirubin level, *mcmol/l*	44.6 (5.2-411.9)	28.6 (7.8-199)	0.64**
Preoperative serum direct bilirubin level *mcmol/l*	19 (1.5-298.1)	16 (2.1-139.2)	0.65**
Operating time, *min*	283 (53.7)	316.6 (23.7)	0.072*
Estimated blood loss, *ml*	500 (200-1200)	650 (300-2300)	0.058**
Blood transfusion, n (%)	7 (10.6%)	3 (25%)	0.18
Type of pancreatoduodenectomy			1.0
Pylorus-preserving, n (%)	14 (20.9%)	2 (16.7%)	
Standard, n (%)	53 (79.1%)	10 (83.3%)	
Pancreatojejunostomy			0.17
End to side	7 (10.4%)	3 (25%)	
End to end	60 (89.6%)	9 (75%)	
Pancreatic duct stenting	6 (9%)	4 (33.3%)	0.04
Serum amylase level of postoperative day 1	75.3 (9-855.9)	280.6 (35.6-725.1)	0.17**
Mortality, n (%)	1 (1.5%)	3 (25%)	0.01
Morbidity, n (%)	19 (28.4%)	12 (100%)	0.001
Relaparotomy, n (%)	1 (1.5%)	5 (41.7%)	0.001
Postoperative length of stay	12 (7-27)	22 (16-35)	0.001**

Notes: * – *values are presented as mean (± standard deviation),*
** – *values are presented as median (interquartile range).*

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TABLE 3.

Univariate regression analysis of risk factors for clinically relevant pancreatic fistula

Variable	OR (95% CI)	p
Age >59 years	0.65 (0.18-2.26)	0.50
Gender (Male)	2.4 (0.6-9.7)	0.21
Body mass index > 25 *kg/m²*	1.83 (0.52-6.37)	0.34
physical status classification system by American Society of Anesthesiologists ≥ III	1.66 (0.32-8.48)	0.54
Number of major comorbidities > 2	1.01 (0.24-4.27)	0.98
Diabetes mellitus	6.77 (0.84-54.31)	0.072
Primary diagnosis other than pancreatic cancer	0.9 (0.21-3.84)	0.89
Preoperative weight loss ≥ 6*kg*	1.5 (0.41-5.43)	0.53
Jaundice	1.53 (0.37-6.36)	0.55
Preoperative serum amylase level > 100 *IU/L*	0.96 (0.15-5.99)	0.96
Soft consistency of pancreas	1.80 (0.50-6.39)	0.36
Operating time > 285*min*	1.53 (0.44-5.31)	0.5
Estimated blood loss >500*ml*	5.04 (1.24-20.38)	0.023
Blood transfusion	2.81 (0.61-12.89)	0.18
Pylorus preserving / standard pancreatoduodenectomy	1.32 (0.26-6.73)	0.73
Pancreatojejunostomy (end to side)	0.35 (0.76-1.60)	0.17
Pancreatic duct stenting	5.08 (1.17-21.98)	0.03
Serum amylase level on postoperative day 1 > 83.8 *IU/L*	2.23 (0.5-9.83)	0.29**

Hashimoto D et al., 2014]. Cloyd J.M. and co-authors (2014) assumed that elevated preoperative serum amylase level correlates with pancreatic fistula after surgery. El Nakeeb A. and co-authors (2014) reported on an increased rate of pancreatic fistula in overweight and obese patients (BMI > 25). However, the study did not reveal any association between pancreatic fistula and preoperative variables. Despite a role in univariate analysis, diabetes mellitus was not a significant predictor for pancreatic fistula in multivariate model (p=0.094).

Recently, several studies concluded that the risk of pancreatic fistula is significantly lower in patients with hard pancreatic texture, resulted by fibrosis due to decreased function of exocrine pancreas and safety of the pancreatic anastomosis. Accordingly, the soft pancreatic texture was considered a valuable prognostic factor for pancreatic fistula [*Lin J et al., 2004; El Nakeeb A et al., 2013; Ridolfi C et al., 2014*]. Pancreatic cancer, leading to obstruction of the pancreatic duct and subsequent pancreatitis, has been reportedly associated with reduced rate of pancreatic fistula, though it increases in case of other periampullary malignancies [*Lin J et al., 2004; de Castro S et al., 2005; Pratt W et al., 2008; Cloyd J et al., 2014*]. Nevertheless, the results of the study cannot confirm the predictive value of primary diagnosis and pancreatic consistency for pancreatic fistula after pancreatoduodenectomy.

TABLE 4.

Multivariate analysis of predictive factors for clinically relevant pancreatic fistula

Variable	Multivariate	
	OR (95% CI)	p
Diabetes mellitus	0.12 (0.01-1.44)	0.094
Pancreatic duct stenting	0.32 (0.06-1.68)	0.18
Estimated blood loss >500*ml*	6.31 (1.1-35.9)	0.038

Taking into account the vulnerability of pancreas, an extensive scrutiny of the appropriate technique for pancreaticodigestive anastomosis has been applied in order to decrease the rate of pancreatic leakage after surgery. In the randomized controlled trial from Figueras J. and co-authors (2013), pancreato-gastrostomy was associated with lower rates of pancreatic fistula compared to pancreatojejunostomy (11% vs. 33%). However, the majority of

the following studies failed to demonstrate significant difference between these techniques in terms of postoperative pancreatic fistula [*Bassi C et al., 2005b; Duffas J et al., 2005; Wente M et al., 2007*]. Several authors claimed that pancreatic duct stenting may reduce the rate of pancreatic fistula through facilitation of pancreatic anastomosis creation and the smooth outflow of the pancreatic juice after pancreatoduodenectomy [*Wang S et al., 2013*]. Nevertheless, the aforementioned advantages were not evident in a randomized trial from Winter J.M. and co-authors (2006), which did not show improved outcomes in patients with pancreatic stents. According to the study anastomosis had no predictive value, whereas the pancreatic duct stenting led to the formation of a clinically relevant postoperative pancreatic fistula, though the difference was not statistically significant on multivariate analysis.

Pratt W.B. and co-authors (2008) reported that estimated blood loss greater than 1000 *mL* during pancreatoduodenectomy is associated with almost nine times increased risk of developing postoperative pancreatic fistula. Other studies also support this finding and emphasize the predictive value of the intraoperative blood loss [*Lin J et al., 2004; Cheng Q et al., 2007*]. In this study, multivariate analysis of perioperative parameters identified the estimated blood loss as the only independent predictor of pancreatic fistula after pancreatoduodenectomy. According to these results, the patients with estimated blood loss greater than 500*ml* are almost six times more likely to develop fistula compared to those with less than 500*ml*. The authors of the study speculate that local ischemia, developed as a result of impaired blood flow, may slow the recovery of pancreatic anastomosis, thereby leading to the anastomotic insufficiency and formation of pancreatic fistula. However, the mechanism behind the correlation between increased intraoperative bleeding and postoperative pancreatic fistula still remains unclear.

The results of the study demonstrate that estimated blood loss greater than 500*ml* is an independent predictor of clinically relevant pancreatic fistula after pancreatoduodenectomy. A growing experience in performing pancreatoduodenectomy, together with special attention to hemostasis, may decrease the rate of pancreatic fistula. Further studies with extensive experience in the implementation of pancreatoduodenectomy are necessary for the identification of other possible risk factors of pancreatic fistula development.

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