The factors of pancreatic fistula development in patients who underwent classical pancreaticoduodenectomy

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AIM: *Pancreatic fistula (PF) and anastomotic leakage are significant complications of the pancreaticoduodenectomy (PD). The PF is considered as the root cause of other major complications of PD. The aim of the study was to investigate the risk factors underlying PF that occurred after PD and the effects of the PF on postoperative morbidity.*
MATERIAL AND METHODS: *In this study, fifty patients who underwent classic PD were evaluated, retrospectively. Patients were divided into two groups as patients with PF and patients without PF. The following demographical, clinical and operative parameters were collected to evaluate the PF; age, gender, preoperative biochemical parameters, resection type, duration of the operation, patient's comorbidities, amount of perioperative transfusion, localization of the tumour, texture of the residual pancreas, type of the anastomosis and the diameter of the pancreatic duct.*
RESULTS: *A statistically significant relation was found between the texture of the remnant pancreatic parenchyma and PF ($p<0.001$). A significant relation was determined between PF and preoperative ALP, GGT, AST, ALT, hemoglobin levels and length of the hospitalization ($p<0.05$). In this study, we found that mortality, abdominal bleeding, bile leakage, intra-abdominal abscess were associated with reoperation and prolonged hospitalization.*
CONCLUSION: *The lack of internationally accepted definition of a fistula is an important issue. Preoperative high ALP, ALT, AST, GGT values, low hemoglobin values and soft texture of remnant pancreatic tissue were found to be related with PF that occurs after PD. Residual pancreatic tissue has been shown as an independent risk factor.*

KEY WORDS: ISPGF, Pancreaticoduodenectomy, Pancreatic fistula, Risk factors

Introduction

Pancreaticoduodectomy (PD) is a unique and complicated surgical approach that was performed in both malignant and benign diseases of the duodenum, head of the pancreas and periampuller region. In 1935, Allen Whipple published a PD series and this operation was called the Whipple procedure as of this date[1]. Pancreatic fistula (PF); is the most common major morbidity that occurs subsequent to pancreatic resections. With increasing surgical experience in recent years, mortality after pancreatic resections has reduced below 6%, with no change in postoperative morbidity rates [2]. According to recent studies, the PF ratio varies from zero to 25% [3]. It is necessary to identify risk factors to prevent the development of PF. PF development has been associated with periampullary regional pathology, pancreatic tissue structure, advanced age, sex, diabetes mellitus, coronary artery disease, blood loss, anastomosis techniques, operative time and extensive lymphadenectomy [4,5].
The aim of the study was to evaluate, compare and discuss the risk factors of the PF, that occurs after classical PD.

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Material and Methods

Fifty patients who referred to the Mersin University Hospital Department of Hepatobiliary Surgery for elective PD between January 2008 and January 2015 were included in this study. Patients were divided into two groups as patients with PF and patients without PF. This study was carried out after the approval of the local ethics committee.

Definition Of Pancreatic Fistula

Criteria used in the definition of PF: appearance of PF after PD; the amount of drainage behind the pancreatic anastomosis over three days is greater than 50 ml; and/or the amylase concentration is three times higher than the serum amylase concentrations [6]. PF is also classified according to the International Study Group on Pancreatic Fistula (ISGPF) as no fistula, Grade A, B and C (Table I)[5].

Collected Data

The following demographical, clinical and operative parameters were collected to evaluate the PF: patient age, gender, abdominal pain, presence of jaundice, presence of coronary artery disease, presence of diabetes mellitus, hemoglobin and hematocrit levels, preoperative serum CA19-9, CEA, glucose, albumin, bilirubin, ALT, AST, ALP and GGT levels, duration of operation, amount of perioperative transfusion, localization of tumour, pathology of tumour, pancreatic-enteric anastomosis type, texture of remnant pancreas and pancreatic duct diameter. The patients with total bilirubin levels > 2 mg / dL were considered jaundice, and patients with serum albumin levels between 3.4 g/dL and 4.8 g/dL were determined normal. Coronary artery disease was diagnosed with history of patients, cardiological examination and echocardiography. A perioperative blood transfusion was defined as the amount of erythrocyte suspension given during surgery. The postoperative blood glucose level was also evaluated in this study.

Surgical Techniques

Neoadjuvant chemoradiotherapy was not given to any patient. The PD was performed by the same hepatopancreaticobiliary surgeons using the Mercedes incision. Two reconstruction techniques were used in order to ensure continuity with the pancreatic stump; duct to mucosa as wirsungojejunostomy (WJ) and invaginated pancreaticojejunostomy (PJ). One of these two methods was chosen by the surgeons based on the diameter of the pancreatic duct and the structure of pancreatic parenchyma. The parenchymal structure of the pancreatic stump was evaluated as soft or hard during the surgery and the panreatic duct diameter was evaluated as normal or wide (>3 mm) based on preoperative imaging methods [7]. None of the patients had pancreaticogastrostomy. WJ was performed without using any internal stent. Prophylactic octreotide was not routinely used. Postoperative early and late complications and mortality rates were examined. Hospital mortality was defined as death developing during hospitalization. Intra-abdominal complications that were seen during the postoperative period were: intra-abdominal abscess collection, development of intra-abdominal haemorrhage, wound infection and prolonged gastric emptying time. After the tenth postoperative day, need for nasogastric decompression or vomiting was assumed as a delayed gastric emptying [8].

Statistical Analysis

The operating data were summarized as the mean, standard deviation, median and frequency value. Categorical variables were compared with Chi-square test. Continuous variables Shapiro-Wilk test was used for testing normality

Table I - *ISGPF (International Study Group On Pancreatic Fistula) definition*

Criteria	Pancreatic Fistula Grade			
	No fistula	Grade a	Grade b	Grade c
Drain / serum amylase ratio	< 3 times	> 3 times	> 3 times	> 3 times
Clinical conditions	Well	Well	Often well	Ill appearing/bad
Specific treatment	No	No	No/yes	Yes
USG/CT* findings	Negative	Negative	Negative/positive	Positive
Persistent drainage (>3 week)	No	No	Usually yes	Yes
Sign of infection	No	No	Yes	Yes
Sepsis	No	No	No	Yes
Reoperation	No	No	No	Yes
Death related to fistula	No	No	No	Yes
Readmission	No	No	Yes/no	Yes/no

*USG: Ultrasound, CT: Computed tomography

of the continuous variables. The relation with the PF andage and duration of the operation were compared with independent *t* test and Mann- Whitney U test. All statistical analyses were performed with the STATA/MP11 program. Alpha significance level less than 0.05 was considered as statistically significant.

Results

PF was developed in 24 (48%) of 50 patients who underwent PD operation. The patients who were included in the study were 37 males and13 females, with a mean age of 62±2,5. The mean age was similar to that of patients with PF (61±12) compared to those without PF (65±10). PF rate was similar in both males and females (p=0.075). The indications for PD operation were: ampullary carcinomas in 16 (32%) patients, pancreatic head tumour in 15 (30%) patients, distal cholangiocarcinomas in 8 (16%) patients, duodenal malignancy in 9 (18%) patients, chronic pancreatitis in 2 (4%) patients. While the mean postoperative length of hospitalization was 15±9 days without PF group, it was 19±9 days with PF group. The length of hospitalization significantly increased in patients who developed PF (p=0.005). Median operative time, however, was comparatively longer than in the PF group (340 minutes versus 399 minutes, p>0.05). Two types reconstruction for pancreatic anastomosis were performed. A WJ was performed in 26 patients, and an invaginated PJ was performed in 24 patients (p=0,160). A total of 24 (48%) patients were diagnosed with PF, with 13 (54.16%) classified as grade A, 3 (12.5%) classified as grade B, and 8 (33.3%) classified as grade C. The total mortality rate among the study population was 10 % (5/50). When the relationship of PF with following demographic and clinical variables were examined, there was no statistical significance: patient age, gender, presence of coronary artery disease, serum CA19-9 and CEA level, history of jaundice, serum albumin and bilirubin level, operative blood loss volume, length of operation time, anastomosis technique, amount of perioperative transfusion, localization of tumour, pathology of tumour and pancreatic duct diameter no statistical significance was found (Table 2). However, statistically significant relation was found between the PF and preoperative high ALP, ALT, AST, GGT values and low hemoglobin values (p<0.05) (Table II). Besides, we found that the structure of the residual pancreatic tissue was statically significant in its association with PF. The pancreatic leak rate was 20.8% in patients who had a hard pancreatic tissue, and was 75.0% in those who had a soft pancreatic tissue (p<0.001). Structure of the residual pancreas was shown to be an independent risk factor. Patients with soft pancreas tissues were under high risk of pancreatic leakage. On the other hand, 25 (50%) were detected in normal sized ducts whereas 25 of the cases (50%) had larger (>3mm) pancreatic duct (of wirsung) diameter,. There was no statistically significant correlation between PF and pancreatic duct diameter (p=0.258)

TABLE II - *Relationship between preoperative biochemical parameters and PF*

Parameters			Pancreatic fistula Yes (24)	No (26)	p
ALP* (30-230U/L)	high	11	5	21	0,024*
	normal	13			
GGT*(<49U/L)	high	9	4	22	0,030*
	normal	15			
Hemoglobin (12,6-17,4 g/dl)	low	12	20	6	0,048*
	normal	12			
Htc*(37-51 %)	low	11	8	18	0,273
	normal	13			
ALT*(<41U/L)	high	10	4	22	0,019*
	normal	14			
AST*(<38U/L)	high	11	5	21	0,024*
	normal	13			
Glucose (>110)	high	6	2	24	0,095
	normal	18			
Ca19-9 (0-27U/mL)	high	12	8	18	1,000
	normal	12			
CEA (0-4,3ng/ml)	high	17	18	8	0,902
	normal	7			

ALP: Alkaline Phosphatase; GGT: Gamma Glutamyl Transferase; Htc: Hematocrit; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; Fisher's Exact test* p<0.05

POSTOPERATIVE OUTCOMES

A total of 14 (28%) patients had no complication while 36 (72%) patients had at least one complication. Besides PF, other postoperative complications were intra-abdominal abscess (16%), intra-abdominal hemorrhage (6%), gastric stasis (4%), gastrojejunostomy leakage (2%), hepaticojejunostomy leakage (2%), wound infection (8%) and delayed gastric emptying (4%).

Discussion

Today PD is the only treatment modality with the potential to cure periampullary tumours. PD is a complex and high-risk surgical approach [9]. The most important complication after PD is PF (6). Duffas et al. reported that mortality rate was 11%, PF rate was 18% [10]. Andivot et al. declared that mortality rate was 5.1% and morbidity was 61%, the PF rate was 13.55% [11], Yang et al. also declared that mortality was 4.8%, PF rate was 16.13% and the mortality associated with PF was 10% [12]. In our study, postoperative mortality rate was 10%,

morbidity and PF rates were 48%. The mortality rate was found to be similar, but the rate of PF was found to be higher than the other studies[1 0-12]. These results might be related with surgical technique. Several facilitator factors were presented in the relevant literature for PF that occurred after PD. Following factors were corralated with PF; age, gender, degree of jaundice, malnutrition, periampullary pathologies, the structure of the pancreatic stump, diameter of pancreatic duct, operation time, type of resection, the technique of pancreatic anastomosis and the amount of intraoperative tranfusion [13]. In the recent studies, the surgeon's experience and prophylactic somatostatin usage have been also reported among the factors affecting PF [14]. In our study, somatostatin analogues were not used prophylactically. In this study, the relationship between PF and preoperative elevated ALP, ALT, AST, GGT rates were found to be significant (p<0,05) (Table II). These high laboratory levels might be related with obstructive jaundice. Obstructive jaundice may induce bacterial translocation and sepsis, with cholestasis and impairment of hepatic synthesis [15]. This mechanism has been suggested as one of the underlying factors in the development of PF. The levels of these enzymes can be reduced with preoperative biliary drainage and the drainage can secure the anastomosis. However, there is still a conflict between the incidence of PF and preoperative biliary drainage [16]. Aranha et al. reported that no difference existed in the incidence of PF in patients who underwent endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC). However, they indicated an increase in the PF in those patients who did not have preoperative stents [17]. Lin et al. showed that no difference in the PF in those patients who did not have preoperative stents [4]. Yeh et al. declared that increased intraoperative haemorrhage was an independent factor for PF risk after PD [18]. In this study, 50 patients, who were perioperatively given at least 2 units of erythrocyte suspension, did not show a significant difference in terms of PF compared with the others (p=0.170). However, a statistically significant correlation was found between preoperative low hemoglobin value and PF (p=0.048), which might be related to the chronic anemia caused by periampullary tumours. Fu SJ et al. reported that lower diameters of pancreatic duct (≤ 3 mm) and the type of the PJ were risk factors for PF occurance [19]. Previous studies have shown that pancreaticogastrostomy has a significantly lower PF rate than PJ [11]. However, pancreaticogastrostomy is not routinely performed in our clinic. Our results showed that there was no statistical significance between pancreatic duct diameter and PF (p=0.258). WJ is technically very difficult and it has been recommended in patients with pancreatic duct dilatation in previous years. However, nowadays, WJ can be applied irrespective of the diameter of the pancreatic duct [20]. Anastomosis types that are performed during the surgery has also been cited as a predictor of PF [18]. Berger et al. reported that PJ invagination technique performed after PD had fewer PF rates than WJ [21]. However, Schmidt et al.[22] and Bartoli et al. [23] reported that the rate of PF development in WJ-treated patients was lowest compared to other anastomoses. We performed WJ to 26 patients, PJ to 24 patients. PF was observed in 10 of WJ patients (38.5%) and 14 of PJ patients (58.3%). Statistically significant difference has not been found between PF and anastomosis type (p = 0,160). As the pancreatic duct diameter plays an important role in determining which PJ technique to choose, some studies have concluded that this parameter is also an independent risk factor for post-PD PF development [19]. Nevertheless, there was no statistically significant difference between PF and pancreatic duct diameter (p=0,258) in our study. Soft pancreas tissue is one of the strong risk factors for development of PF [11]. In our study, the pancreas tissue of 24 patients was soft. PF was observed in 18 (75%) of the patients with soft pancreatic tissue. Statistical significance was found between the texture of pancreatic tissue and PF (p <0.001).When the literature is reviewed, it is seen that these two factors have been evaluated as significant risk factors [24]. Soft residual pancreatic tissue and narrow duct size have been accepted as a potent PF risk factor [25]. Yang et al. reported that the PF rate was 4.9% patients who had pancreatic duct diameter ≥3 mm, and was 38.1% who had pancreatic duct diameter < 3 mm (p = 0.002). They also reported that PF rate was 2.9% who had hard pancreas, and was 32.1% in those who had soft pancreas (p = 0.004) [12]. Yeo et al. reported that, in patients with chronic pancreatitis, the fibrotic formation of pancreatic tissue has facilitated PJ anastomosis while the parenchymal tissue of a soft and brittle pancreas has seriously complicated the anastomosis [26]. Suziki et al. reported that internal or external drainage with a pancreatic duct stent to reduce PF was not beneficial [27]. In our study, no stents were used. The inhibition of the exocrine secretion of the pancreas is thought to reduce the rate of PF after PD [28]. Especially in recent years, the use of prophylactic somatostatin after PD has been emphasized, but no consensus has been made [29]. Poon et al. have analysed six prospective randomized trials that were conducted between January 1990 and December 2000 and have found no beneficial effect of the prophylactic octreotide usage [5]. In our study, somatostatin analogues were not used.

To reduce the risk of PJ anastomotic leak, the pancreatic duct ligation without anastomosis is preferred in some patients However, since the external fistula rate was on average 50%, this method was abandoned [24,30]. In the studies that the pancreatic duct was blocked with biological substances, the results were reported as quite successful. For example, fibrin-glue was applied around the anastomosis in some of the patients who had possible anastomosis leakage determined by the surgeon during surgery. The PF rates were respectively 26% and 30%

in the fibrin glue patients and in the control group. Therefore, the difference between two groups was not statistically significant [31]. Tian Y et al. performed another technique 'omental flap around anastomosis' which also did not prevent PF [32]. PD is a complex process and requires multiple organ resections and anastomosis. For this reason, postoperative complications cannot be attributed to a single cause and it is assumed that each procedure itself is a risk factor. Although PF is not solely responsible for complications, activation of enzymes secreted from pancreatic leaks are thought to lead to auto-digestion, which is caused to intraabdominal collection, intraabdominal abscess, prolonged gastric emptying and postoperative bleeding. Prolonged hospitalization and several other major complications were associated with PF. In this study, we found that PF is related with mortality, abdominal hemorrhage, biliary leakage, intra-abdominal abscess, pneumonia, reoperation and prolonged hospitalization. The first preferred treatment for PF is not surgery. Endoscopic and percutaneous treatments are important therapeutic modalities. Surgical intervention may be required in selected cases. In our study, in most of the patients with PF, the fistula were closed with conservative methods and percutaneous drainage therapy. Two patients with Grade C had relaparotomy. Being a retrospective study was the limitation of this study.

Conclusion

Many risk factors may have a role in PF occurance after classical PD. Lack of internationally accepted definition of fistula causes important confusion. This might be a reason of the variated PF rates and different risk factors determinations in various studies. We found that preoperative high ALP, ALT, AST, GGT values, low hemoglobin values and soft texture of remnant pancreatic tissue were statistically significant in PF development among PD patients.

Riassunto

La fistola pancreatica (PF) e la deiscenza anastomotica sono importanti complicanze possibili della duodenopancreatectomia (PD) ed è considerata la causa principale di altre importanti complicanze dell'intervento. Ci siamo proposti di studiare i fattori di rischio alla base della PF che si sono verificati dopo la PD e gli effetti della PF sulla morbilità postoperatoria nella nostra esperienza.

Per questi studio sono stati valutati retrospettivamente cinquanta pazienti sottoposti a PD classica. I pazienti sono stati divisi in due gruppi, con PF e senza PF. Sono stati considerati i seguenti parametri demografici, clinici e operativiper valutare la PF: età, sesso, parametri biochimici preoperatori, tipo di resezione, durata dell'operazione, comorbidità del paziente, quantità di trasfusione perioperatoria, localizzazione del tumore, consistenza del pancreas residuo, tipo di anastomosi e diametro del dotto pancreatico.

È stata trovata una relazione statisticamente significativa tra la struttura del parenchima pancreatico residuo e la PF (p <0,001). È stata riscontrata una relazione significativa tra PF e ALP, GGT, AST, ALT, livelli di emoglobina e durata del ricovero (p <0,05) preoperatori. In questo studio, abbiamo scoperto che la mortalità, il sanguinamento addominale, la perdita biliare, l'ascesso intraaddominale erano associati al reintervento e al ricovero prolungato.

La mancanza di una definizione di fistola accettata a livello internazionale è una questione importante. Alti valori preoperatori di ALP, ALT, AST, GGT, bassi valori di emoglobina e consistenza morbida del tessuto pancreatico residuo sono risultati correlati con la PF che si verifica dopo la PD. Il tessuto pancreatico residuo è stato mostrato come un fattore di rischio indipendente.

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