

Impact of possible risk factors on pancreatic fistula development after pancreaticoduodenectomy: Prospective cohort study

Pankreatikoduodenektomi sonrası olası risk faktörlerinin pankreatik fistül gelişimi üzerine etkisi: Prospektif kohort çalışma

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Ethics Committee Approval: This study is approved by Ministry of Health, Istanbul Goztepe Training and Research Hospital Ethical Committee with the decision number 54/D, dated 2/10/2009. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Etik Kurul Onayı: Bu çalışma SB İstanbul Göztepe Eğitim ve Araştırma Hastanesi Etik Kurulu tarafından 10.02.2009 tarihli 54/D karar numaralı ile onaylanmıştır. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 3/27/2020

Yayın Tarihi: 27.03.2020

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Abstract

Aim: The most important complication that develops after pancreaticoduodenectomy is anastomosis leak and pancreatic fistula. Pancreatic fistula is thought to be the cause of major complications such as intra-abdominal abscess. The relationship between the development of fistula after pancreaticoduodenectomy and intraoperative risk factors (resection type, pancreatic anastomosis type, pancreatic duct diameter and pancreatic stump structure), along with the effect of pancreatic fistula on morbidity were investigated.

Methods: Forty-one patients who had undergone pancreaticoduodenectomy due to periampullary region tumors were included in this study. Patients were divided into two groups as with and without pancreatic fistula, and compared in terms of demographics, preoperative serum bilirubin and serum albumin values, and intraoperative risks (resection type, pancreatic anastomosis type, pancreatic duct diameter and pancreatic stump structure). In addition, the groups were evaluated for the development of post-operative complications.

Results: When both groups were compared in terms of intraoperative risk factors (resection type, pancreatic anastomosis type, pancreatic duct diameter and pancreatic stump structure), similar results were obtained for biochemical parameters ($P=0.719$, 0.599 , 0.250 , 0.906 , respectively). A statistically significant association was found between the occurrence of pancreatic fistula and delay of gastric emptying ($P=0.028$). No significant relationship was detected between intraabdominal collection-abscess, intraabdominal hemorrhage, wound infection parameters and pancreatic fistula ($P=0.204$, 0.950 , 0.116 , respectively).

Conclusion: No factors were found to be solely associated with the development of pancreatic fistula following pancreaticoduodenectomy; however, it was concluded that pancreaticoenteric anastomosis technique and the consistency of pancreatic stump may be closely and significantly related.

Keywords: Pancreatic fistula, Pancreaticoduodenectomy, Pancreaticoenteric anastomosis

Öz

Amaç: Pankreatikoduodenektomi sonrası gelişen en önemli komplikasyon anastomoz kaçağı ve pankreas fistülüdür. Pankreas fistülünün karın içi apse gibi büyük komplikasyonların nedeni olduğu düşünülmektedir. Pankreatikoduodenektomi sonrası fistül gelişimi ile intraoperatif risk faktörleri (rezeksiyon tipi, pankreatik anastomoz tipi, pankreatik kanal çapı ve pankreatik güdük yapısı) arasındaki ilişki araştırıldı ve pankreatik fistülün morbidite üzerine etkisi araştırıldı.

Yöntemler: Bu çalışmada, periampuller bölge tümörleri nedeni ile pankreatikoduodenektomi operasyonu uygulanan 41 hasta incelendi. Hastalar pankreatik anastomoz kaçağı olan ve olmayan olarak iki gruba ayrıldı. Her iki grup yüksek serum bilirübin ve düşük serum albumin değerleri ve intraoperatif riskler (rezeksiyon tipi, pankreatik anastomoz tipi, pankreatik kanal çapı ve pankreatik güdük yapısı) açısından karşılaştırıldı. Ayrıca gruplar post-operatif komplikasyon gelişimi açısından da değerlendirildi. Postoperatif komplikasyonlar: İntraabdominal koleksiyon-apse, intraabdominal hemoraji, yara yeri enfeksiyonu ve mide boşalma süresinin uzaması olarak kabul edildi.

Bulgular: Her iki grup da intraoperatif risk faktörleri (rezeksiyon tipi, pankreatik anastomoz tipi, pankreatik kanal çapı ve pankreatik güdük yapısı) açısından karşılaştırıldığında, biyokimyasal parametreler için benzer sonuçlar elde edilmiştir. ($P=0,719$, $0,599$, $0,250$, $0,906$ sırasıyla). Gruplar, postoperatif komplikasyon parametreleri ile kıyaslandığında ise pankreatik fistül ile mide boşalma süresinin gecikmesi arasında istatistiksel olarak anlamlılık tespit edildi ($P=0,028$). İntra-abdominal apse, karın içi kanama, yara enfeksiyonu parametreleri ve pankreatik fistül arasında istatistiksel olarak anlamlı bir fark bulunmadı (sırasıyla $P=0,204$, $0,950$, $0,116$).

Sonuç: Pankreatikoduodenektomi sonrası pankreatik fistül gelişiminde hiçbir faktör tek başına etkili bulunmadı. Ancak belirgin bir şekilde pankreatikoenterik anastomoz tekniği ve pankreatik güdüğün kıvamı ile yakından ilişkili olabileceği kanaatine varıldı.

Anahtar kelimeler: Pankreatik fistül, Pankreatikoduodenektomi, Pankreatikoenterik anastomoz

Introduction

Pancreaticoduodenectomy (PD) is the only and a complex approach, which is believed to provide cure in the treatment of periampullary region tumors. Ever since PD series was published by Allen Whipple in 1935, this operation has been called the "Whipple Operation". In 1978, Pylorus-preserving pancreaticoduodenectomy (PPPD) was described by Longmire and Traverso [1,2]. Today, PPPD became more preferred than the standard Whipple intervention in periampullary malignity [3]. Besides providing a cure as much as the standard Whipple procedure, PPPD is also reported to have many advantages over Whipple surgery in terms of quality of life in the postoperative period [1,4]. 50-70% of periampullary region carcinomas originate from the pancreas, 15-25% from ampulla of Vater, 10% from duodenum, and 10% from the choledoch. Although ductus cells constitute 4% of all pancreas cells, more than 90% of exocrine cancers of pancreas are the adenocarcinomas, which originate from ductal epithelia [5]. The most crucial complication following PD is the development of pancreatic fistula (PF) since it can cause other complications. Activation of enzymes secreted from pancreatic leakage causes autodigestion, which leads to peripancreatic collection, intraabdominal abscess, delay of gastric emptying, and postoperative hemorrhage. PF ratio was reported in a wide range between 2-50%, the reason for which lies in the lack of an internationally accepted definition of fistula [1]. The most important risk factor in PF development is the pancreatic stump. If the protease enzymes secreted from this tissue are activated, they may digest the surrounding tissues, and cause partial or full diastasis of anastomosis. The fistulisation of pancreatico-enteric anastomosis leads to increased inflammation in the surrounding tissues, and even dramatic erosion of main veins in the retroperitoneal region. In such cases, complications such as intraabdominal and retroperitoneal collection, and delay of gastric emptying are mostly observed as the cause of hemorrhagic phenomenon. Intraabdominal abscess is closely related with pancreatic anastomosis leakage, and at least 50-60% of the abscesses develop upon pancreatic anastomosis leakage. All these complications lead to the development of sepsis, shock, single or multiple organ failure, or death [6]. Herein, we investigated the relationship between the development of fistula after pancreaticoduodenectomy and intraoperative risk factors (resection type, pancreatic anastomosis type, pancreatic duct diameter and pancreatic stump structure). In addition, the effect of pancreatic fistula on morbidity was investigated.

Materials and methods

This study was conducted in accordance with guidelines of the Declaration of Helsinki following the approval of the ethics committee of Ministry of Health, Istanbul Goztepe Training and Research Hospital (Decision number: 54/D, dated 2/10/2009). The patients, who had undergone PD due to periampullary region tumors between April 1996 and December 2008 at Istanbul Goztepe Training and Research Hospital, in the 4th General Surgery Clinic, were included in the study. Resection types were divided into two groups as standard PD and PPPD techniques. Cases in which total pancreatectomy is performed, are excluded from the study.

Forty-one patients were included in the study, sixteen of which were females. Standard PD and PPPD operations were performed in 20 and 21 patients, respectively. The patients were evaluated based on the type of PJ (invagination type or mucosal type), consistency of pancreatic stump (hard or soft) and dilation of the pancreatic duct (dilated or not dilated). The International Study Group of Pancreatic Fistula definition and grading of postoperative pancreatic fistula has been used in this study. The patients were divided into two groups as those with and without pancreatic fistula. The patients were examined in terms of intra-abdominal abscess, delay in gastric emptying time, wound infection, and intra-abdominal hemorrhage, as the main causes of morbidity.

Patients' age and gender distribution, symptoms and symptom frequency in the preoperative period, localization of tumor, preferred surgical techniques, postoperative early and late period complications, and mortality rates were investigated.

Statistical analysis

NCSS 2007&PASS 2008 Statistical Software (Utah, USA) program was used for statistical analysis. Besides descriptive statistical methods (mean, standard deviation, frequency), Chi-Square and Fisher's Exact tests were used for the comparison of qualitative data. The results were evaluated within a 95% confidence interval, and the significance was evaluated at $P < 0.05$ level.

Results

Forty-one patients who had undergone PD due to periampullary region tumors between April 1996 and December 2008 were included in this study. The patients were followed for two years. Ages of the patients ranged between 15 and 75 years. There were 16 (39%) females and 25 (61%) males. The mean age of all patients was 61.92 (11.16) years. The tumor was located in the head of pancreas in 20 patients (48.8%), in the ampulla of Vater in 11 (26.8%), in the distal choledoch in 4 (9.8%), and in the duodenum in 2 patients (4.9%). One of the patients had a pancreatic cystadenoma (2.4%), one had chronic pancreatitis (2.4%), one had a pancreatic mass (2.4%), and one had an ampullary adenoma (2.4%) (Table 1).

While the preoperative serum albumin levels of 24 patients (58.5%) were normal, that of 17 patients (41.5%) were low. Serum bilirubin levels were high in 32 patients (78%) and normal in 9 (22%). No statistically significant relationship was detected between the development of a pancreatic fistula, low serum albumin levels ($P=0.837$) or high serum bilirubin levels ($P=0.350$) in the preoperative period (Table 2).

Standard PD technique (Whipple Operation) and PPPD were performed in 21 (51.2%) and 20 patients (48.8%), respectively. Evaluation of pancreatic anastomosis types revealed that invagination-style pancreaticojejunostomy (PJ) was performed 29 patients (70.7%) while PJ was done between the ductus and the mucosa in 12 (29.3%). While the parenchyma tissue of pancreatic stump was soft in 16 patients (39%), it was determined as hard in 25 (61%). The diameter of pancreatic duct (Wirsung) was dilated (≥ 3 mm) in 28 cases (68.3%), and not dilated in 13 (31.7%) (< 3 mm).

There was no statistically significant relationship between the development of pancreatic fistula and PD resection

type ($P=0.719$), pancreaticoenteric anastomosis type ($P=0.599$), the parenchyma structure of the pancreatic stump ($P=0.250$) or the diameter of pancreatic duct ($P=0.906$) (Table 3).

Regarding the distribution of morbidity rates after the operation, 9 patients (42.8%) had PF, 4 patients (19.0%) had intraabdominal collection-abscess, 4 had extended gastric emptying time (19.0%), 3 had wound site infection (14.2%), and one patient (4.7%) had intraabdominal hemorrhage. No statistically significant relationship was determined between the PF development and development of intraabdominal collection and/or abscess, intraabdominal hemorrhage, or wound site infection within the following period ($P=0.204$, 0.950, 0.116 respectively). The difference between PF incidence rates between patients with longer and normal gastric emptying times were statistically significant ($P=0.028$) (Table 4).

Table 1: Distribution of patients' pathologic diagnosis

Pathologic diagnosis	n (41)	%
Tumor on pancreas head	20	48.8
Tumor on ampulla of Vater	11	26.8
Distal choledochal tumor	4	9.8
Duodenum tumor	2	4.9
Chronic pancreatitis	1	2.4
Pancreatic cystadenoma	1	2.4
Fibromatosis neoplasia	1	2.4
Ampulla adenoma	1	2.4

Table 2: Biochemical general risk factors in pancreatic fistula development evaluation

		Pancreatic fistula		P-value
		Present n (%)	Absent n (%)	
Bilirubin Level	High	6 (18.8%)	26 (81.3%)	0.350
	Normal	3 (33.3%)	6 (66.7%)	
Albumin Level	Normal	5 (20.8%)	19 (79.2%)	0.837
	Low	4 (23.5%)	13 (76.5%)	

Chi-square test, Fisher's Exact test

Table 3: Comparison of intraoperative factors, which are considered as having effects on development of pancreatic fistula

Parameters		Pancreatic fistula		P-value
		Present n (%)	Absent n (%)	
Resection type	Standard PD	4 (19.0)	17 (81.0)	0.719
	PPPD	5 (25.0)	15 (75.0)	
Anastomosis type	Invagination type PJ	7 (24.1)	22 (75.9)	0.599
	Duct-to-Mucosa PJ	2 (16.7)	10 (83.3)	
Parenchyma structure of pancreas stump	Soft	5 (31.3)	11 (68.8)	0.250
	Hard	4 (16.0)	21 (84.0)	
Diameter of pancreatic duct	Dilated >3 mm	6 (21.4)	22 (78.6)	0.906
	Nondilated <3 mm	3 (23.1)	10 (76.9)	

Chi-square test, Fisher's Exact test

Table 4: Comparison of complications which was developed after operation

Parameters		Pancreatic fistula		P-value
		Present n (%)	Absent n (%)	
Intraabdominal collection/abscess	Present	2 (50.0)	2 (50.0)	0.204
	Absent	7 (18.9)	30 (81.1)	
Intraabdominal hemorrhage	Present	0 (0)	1 (100)	1.000
	Absent	9 (22.5)	31 (77.5)	
Wound site infection	Present	2 (66.7)	1 (33.3)	0.116
	Absent	7 (18.4)	31 (81.6)	
Gastric emptying time	Normal	6 (16.2)	31 (83.8)	0.028
	Extended	3 (75.0)	1 (25.0)	

Fisher's Exact test

Discussion

Today, the only potentially curative treatment type in periampullary tumors is PD. It is a highly complex and risky surgical approach. PD has become a routine method at experienced centers, and the mortality rate significantly reduced within the last 2 decades. Patient selection, increased surgical experience, development of preoperative and postoperative follow ups, and multidisciplinary approach allowed us to achieve better results. Nevertheless, the mortality is still 3-5% even in experienced centers, and the total morbidity is reportedly between 30-50%. This leads to increased hospitalization and cost [1].

The most important complication of PD is the development of a pancreatic fistula, which is thought to induce the development of other complications. PF is reported as 2-50% [1,6]. This wide range is due to the lack of an internationally accepted definition of a fistula [6]. In the study conducted by Duffas et al. [7], mortality and PF rates were 11% and 18%, respectively. The mortality, morbidity and PF rates reported by Andivot et al. [8] were 5.08%, 61% and 13.5%, respectively. Yang et al. [9] stated that the mortality, morbidity, and PF rates were 4.8%, 43.5% and 16.1%, respectively, while the evaluations of Fang WL et al. [10] yielded mortality, morbidity and PF rates of 8.9%, 56.4% and 17.6%, respectively. Our results were comparable to those reported in the literature.

Following PD, many risk factors for the development of PF were discussed in the literature: Among them are age, gender, degree of hepatitis, malnutrition, pathology of periampullary region tumor, resected part of the pancreas, consistency of the pancreatic stump, width of the pancreatic duct, time of operation, resection type, techniques of pancreatic anastomosis, and intraoperative hemorrhage [1,9]. Furthermore, novel studies in the literature reported the experience of the surgeon and the use of prophylactic somatostatin among the factors affecting PF [1,6,10]. High serum bilirubin and low albumin values were found not to pose a risk for PF development [1,11], just as in our study. Yeo CJ et al. [6] reported that preoperative low albumin value, which is not specific for PF, increases the complication rate for surgical procedures. Likewise, it has been reported that with a significantly high serum bilirubin level in the preoperative period, it may cause impaired liver, kidney, and immune systems, and increase the postoperative morbidity and mortality [12]. It was concluded that the used resection type was not a risk factor regarding the development of PF. Comparison with the literature revealed that the results were similar [9,13].

Kim et al. [14] found that PF rate was 3.2% in the group with wirsungojejunostomy and 17.5% in the group with intussusception. In addition, during postoperative follow-up, it was observed that the diameter of the pancreatic duct increased, and the pancreatic thickness decreased significantly in the intussusception group [14]. Poon et al. [15] found wirsungojejunostomy type anastomosis technique more effective than the invagination type. Marcus et al. [16] did not find wirsungojejunostomy anastomosis technique safe. They found the intussusception technique safer. In our study, 7 (24.1%) of 29 patients who underwent invagination type PJ developed PF, while 2 (16.7%) of 12 patients who underwent wirsungojejunostomy developed fistula. Although there was a difference between PJ and wirsungojejunostomy techniques in terms of PF development, it was not statistically significant. This result may be related to the scarcity of patients undergoing wirsungojejunostomy.

When the literature is examined, it was seen that the stiffness of the pancreatic stump tissue is considered as an important risk factor. Yang et al. [9] found the consistency of the remaining pancreatic tissue and the width of the pancreatic duct were related to the development of PF. PF rate was 4.8% in pancreatic duct widths of 3 mm and above, and 38.1% in those narrower than 3 mm. The rate of fistula development was 2.9% in patients with stiff remaining tissues, and 32.1% in soft ones.

Similarly, Yeo et al. [11] determined that there is a strong relationship between the structure of the remaining pancreatic tissue and PF. In his studies, none of 53 patients with hard pancreatic tissues (0%) developed fistula, while 19 of 75 (25%) patients with soft pancreatic tissue did. In conclusion, while fibrotic pancreatic tissue significantly facilitates pancreatico-enteric anastomosis in patients with chronic pancreatitis, it has been concluded that soft pancreatic parenchyma significantly complicates anastomosis [11]. Suziki et al. [17] determined the PF rate as 5 in 50 patients (8%) with their anastomosis techniques based on the width of the pancreatic duct and pancreatic tissue type. In our study, 5 (31.3%) of 16 patients with soft pancreatic stump parenchymal tissues and 4 (25.0%) of 25 patients with hard parenchymal tissues developed PF. Pancreatic stump softness caused an increase in the rate of PF development between the two parameters, but was not statistically significant.

Study of Suziki et al. [17] revealed that the internal and external drainage, which is performed by stenting the pancreatic duct to reduce PF after PD, had no benefit. The studies, defending the benefits of stenting, state that the stent shall reduce the damages to be caused by the exocrine secretion of pancreas, and decrease the fistula rate by securing the anastomosis. In some studies, they have found the inconvenience of stenting, and determined that the erosion caused by stent may increase the PF rate. Nonetheless, PF rate was found similar in patients to whom stents were and were not applied [9]. We did not use internal stents to any of our patients in this study.

It was thought that the inhibition of exocrine secretion of pancreas may decrease the PF rate after PD. The use of prophylactic somatostatin after PD has been emphasized in the recent years, however, a consensus could not be established. In the study conducted by Yang et al., while a decrease in PF rate was determined with the use of somatostatin in patients to which distal pancreatectomy and partial pancreatic resection were performed, the advantage of somatostatin use after PD over placebo could not be demonstrated [9]. Yeo et al. [11] performed PD on 211 randomized patients by using somatostatin and saline, and PF rate was determined as 11% in somatostatin group, and 9% in the control group. Yeo et al. [11] have determined that use of prophylactic somatostatin after PD did not decrease the fistula rate. Poon et al. [15] have conducted the meta-analysis of 6 ten-year prospective randomized studies and could not demonstrate any beneficial effects of the use of prophylactic somatostatin.

Limitations

Although pancreatic fistula studies are limited especially in one type of surgical technique, we think that we examined different surgical techniques in different pathologies in this study. We also think that by reflecting intra-operative risks to the study, we have revealed how pancreatic fistula affects morbidity. In the study, we statistically notice that the number of patients is insufficient. Poor identification of patients' comorbidity is one of the weaknesses.

Conclusion

We found that no parameters were effective on pancreatic fistula development in patients undergoing standard PD, PPPD, end-to-end intussusception PJ and end-to-end Wirsungojejunostomy. The insufficient number of patients and many parameters (such as chronic diseases) have not been

evaluated within the boundaries of the study. However, we think that we need larger studies to prove that the low serum albumin, high bilirubin values, the stiffness of the pancreatic parenchymal structure and the diameter of the pancreatic duct are effective in the development of PF.

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