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Postoperative pancreatic fistula after pancreaticoduodenectomy: if you lack knowledge of what to search for, you will be unable to locate what you desire

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Abstract. – OBJECTIVE: Postoperative pancreatic fistula (POPF) is the most common and critical complication of pancreatoduodenectomy (PD). In this study, we aimed to define preoperative, perioperative, and postoperative conditions that may cause POPF and examine the predictive value of drain fluid amylase (DFA) values in showing the clinical severity of POPF.

PATIENTS AND METHODS: Between December 2018 and December 2019, 49 patients who underwent PD for malignant reasons by a single team were retrospectively analyzed. Patients with benign indications, vascular reconstruction, preoperative biliary drainage catheterization, resectable liver metastases, POPF that occurred after reoperation, and patients undergoing neoadjuvant oncological treatment were excluded from the study. The patients were divided into two groups developing (FP) and non-developing (FN) POPF.

RESULTS: There was no difference between the groups in terms of gender (p=0.781), age (p=0.219), American Society of Anesthesiologists (ASA) score (p=0.338), and comorbidity status (p=0.219).

The mean body mass index (BMI) kg/m² values of the patients in the FN and FP groups were 25.2±4.0 kg/m² and 27.4±2.6 kg/m², respectively (p=0.042). An increased BMI increases the risk of POPF.

Preoperative prognostic nutritional index (PNI) score (p=0.588), preoperative total bilirubin level (p=0.707), pancreatic duct diameter (p=0.334), pancreatic texture (p=0.334), operation time (p=0.659) do not pose a risk for POPF. Increased perioperative bleeding amounted to a risk for POPF (123.8±46.7 ml, 244.7±66.3 ml in FN and FP groups, respectively, p=0.024). Drain fluid amylase (DFA) values (p<0.001, p=0.043, p=0.019, respectively) were found to be high in patients with POPF on postoperative days 1, 4, and 7.

CONCLUSIONS: Increased BMI and excess perioperative blood loss increase the risk of POPF. DFA level is an easily applicable method that provides early diagnosis for POPF.

Key Words:
Pancreas fistula, POPF, Drain amylase, Drain lipase.

Introduction

Pancreatoduodenectomy (PD) is a challenging surgical procedure associated with high mortality and morbidity. Although improvements in surgical techniques and postoperative care have improved the overall mortality rate (2-14%), postoperative morbidity rates are still significantly high (30-50%)[1,2].

Postoperative pancreatic fistula (POPF) is the most common and critical complication of PD, associated with an increased risk of pseudoaneurysm, postoperative bleeding, and multiple organ failure leading to death. The incidence of POPF development is 5-30%[3]. The development of POPF occurs when the pancreatic enzyme extravasates from the pancreaticoenteric anastomosis to the peripancreatic or intraabdominal area. Many studies[4,5] have attempted to systematically evaluate risk factors for POPF and develop new anastomosis techniques or perioperative care strategies to prevent POPF. However, these procedures could not wholly prevent POPF. Therefore,

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appropriate strategies must be defined to manage POPF after PD and improve post-PD mortality rates.

Placing a drainage tube in the surgical field at the end of PD has two purposes. The first is the detection of any intra-abdominal fluid leakage, usually caused by pancreaticojejunostomy; the second is the drainage of fluid accumulation in the abdomen. The level of amylase can be tested to see if the fluid in the drain is due to pancreatic leakage. If a pancreaticojejunostomy leak is suspected, further screening is done to confirm or rule it out.

In our study, we aimed to define preoperative, perioperative, and postoperative conditions that may cause POPF and examine the predictive value of drain fluid amylase (DFA) values in showing the clinical severity of POPF.

Patients and Methods

Patients who underwent PD for malignant reasons (distal extrahepatic bile duct malignancy and pancreatic head carcinoma) at Izmir Health Science University Tepecik Research and Training Hospital were retrospectively analyzed between December 2018 and December 2019. Patients with benign indications, vascular reconstruction, preoperative biliary drainage catheterization, resectable liver metastases, POPF that occurred after reoperation, and patients undergoing neoadjuvant oncological treatment were excluded from the study.

Patients

Patients were evaluated by the parameters of age, gender, body mass index (BMI), prognostic nutritional index (PNI) score, preoperative bilirubin values, American Society of Anesthesiologists (ASA) scores, biliary drainage status, pancreatic tissue stiffness, pancreatic duct diameter (PDD), perioperative operation data, postoperative (1st, 4th and 7th day) DFA values.

Surgical details were obtained from the prospectively followed patient data sheet, surgery reports, and anesthesia records. Demographic data, surgical details, postoperative data, and pathological data were extracted from the clinical records of the patients. In addition, the surgeon's qualitative intraoperative assessment of pancreatic tissue (soft or hard) was obtained from the operative report. After pancreatic resection, remnant pancreatic tissue was evaluated as "soft" if it was in a normal structure. Previous pancreatitis, desmoplastic reactions, etc. and related conditions were accepted as "hard".

PNI values were calculated according to the formula 10*[serum albumin level (g/dl) + lymphocyte count ratio (mm^3)]. Pancreatic tissue stiffness was classified based on the surgeon's assessment. PDD was determined according to the postoperative pathology reports.

Operational Procedure

Classical PD (not pylorus preserving style, Classical Whipple procedure) was performed on patients. All of the procedures were performed by a single surgeon in our institution and in the same way. For example, the "duct to mucosa" technique was used for pancreatojejunostomy (an internal pancreatic stent was placed in all anastomoses with the same anastomotic technique). In addition, two drains were routinely placed posterior to the hepaticojejunostomy and posterior to the pancreatojejunostomy. "Prophylactic octreotide" was not used to prevent pancreaticojejunostomy leakage.

POPF severity was evaluated according to the consensus report of the "International study group of pancreatic surgeons (ISGPF)" in 2016[3]. The Ethics Committee of Health Science University Tepecik Research and Training Hospital approved the protocol of this study (approval number: 2019-089). Since the study was retrospective, patient consent was not required.

Statistical Analysis

Statistical analyses were performed using SPSS version 17.0 software (SPSS Inc., Chicago, IL, USA). The conformity of the variables to the normal distribution was examined using analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). In descriptive analyses, the variables were given as mean ± standard deviation. Frequency and percentage values of demographic characteristics and categorical variables were given. In continuous data, the Mann-Whitney U test was used to compare binary groups with or without pancreatic fistula. Pearson's Chi-Square or Fisher's Exact Chi-Square test was used to analyze categorical data. Cases with a p-value below 0.05 were considered statistically significant.

Results

Our study included 49 consecutive PD patients. The patients were divided into two groups those

Table I. Compare of pancreatic fistula groups according to preoperative characteristics.

	POPF (-) (n=35)	POPF (+) (n=14)	p
Gender (male)	21	9	0.781
Age (years)	65.1±11.7	69.1±10.3	0.219
BMI (kg/m^2)	25.2±4.0	27.4±2.6	**0.042**
Comorbidity (yes)	24	12	0.218
ASA (1-2)	17	4	0.338
PNI	32.9±7.4	32.3±5.9	0.588
Total bilirubin (g/dl)	7.2±6.8	7.0±7.2	0.70

POPF: Postoperative pancreatic fistula, BMI: Body mass index, ASA: American society of anesthesiologists, PNI: Prognostic Nutrition Index.

Table II. Comparison of perioperative characteristics of both groups.

	POPF (-) (n=35)	POPF (+) (n=14)	p
Duration of operation (min)	202.4±51.6	261.8±73.1	0.659
Amount of bleeding (mL)	123.8±46.7	244.7±66.3	**0.024**
Need for transfusion (n)	3	3	0.659
Pancreatic density (soft)	21	10	0.453
Pancreatic duct diameter (mm)	6.3±1.9	5.9±1.6	0.588

POPF: Postoperative pancreatic fistula.

who developed a fistula (FP) and those who did not (FN).

Of the patients, 30 (61.2%) were males, and 19 (38.8%) were females. The mean age of all patients was 66.2±11.4 years. There was no statistically significant difference between the groups in terms of gender (p=0.781), age (p=0.219), ASA score (p=0.338), and comorbidity status (p=0.219).

The mean BMI values of the patients in the FN and FP groups were 25.2±4.0 kg/m^2 and 27.4±2.6 kg/m^2, respectively (p=0.042). An increased BMI poses a risk for the development of POPF. The preoperative and perioperative data of the patients are summarized in Tables I and II, respectively.

The mean PNI score of the patients in the FN group was 32.9±7.4, and the mean PNI score of the patients with FP was 32.3±5.9. No statistical difference was found when the two groups were compared according to their PNI scores (p=0.588).

Preoperative total bilirubin values were compared between the two groups. The mean bilirubin values of the FN and FP groups on the morning of the operation were 7.2±6.8 g/dl and 7±7.2 g/dl, respectively. The total bilirubin value was not statistically different between the two groups (p=0.707).

Perioperative pancreatic tissue was divided by the operating surgeon into two groups as hard and soft [pancreatic tissue was evaluated as soft in 18 (36.7%) patients and as hard in 31 (63.3%) patients]. Pancreatic fistula developed in 10 (32.2%) patients with hard pancreatic tissue and four (22.2%) patients with soft tissue, and no significant correlation was found between pancreatic texture and POPF development (p=0.453).

PDD was accepted as 3 mm as usual. The mean PDD was 6.3±1.9 mm and 5.4±2 mm in the FN and FP groups, respectively. PDD was not statistically associated with POPF (p=0.166). There was no significant difference in POPF between patients with a pancreatic duct diameter greater than or below 3 mm (p=0.334).

There was no correlation between operation time and POPF (202.4±51.6 min, 202.4±51.6 min, p=0.659 in FN and FP groups, respectively). Increased perioperative bleeding amounted to a risk for POPF (123.8±46.7 ml, 244.7±66.3 ml in FN and FP groups, respectively, p=0.024).

POPF developed in 14 patients (28.5%). 8 (57.1%) patients with pancreatic fistula Grade A, 4 (28.5%) patients with Grade B, and 2 (14.2%) patients with Grade C. In patients with POPF, drain fluid amylase (p<0.001, p=0.043, p=0.019, respectively) values were found to be high on postoperative 1st, 4th, and 7th days. The presence of POPF did not increase the rate of wound infection (p=0.453), delayed gastric emptying (p=0.334), and reoperation (p=0.653). The overall mortality rate was 22.4% (n=11). The mean hospital stay was 15.9±8.7 days.

Discussion

Despite advances in medicine and technical changes that have occurred in the last few decades, POPF remains the most common complication after PD. The emergence of POPF generally leads to a prolonged hospital stay and the need for more radiological, endoscopic, or surgical interventions and is a common cause of surgical mortality[6,7].

Considering the importance of POPF according to patient outcomes, researchers[8,9] tried to identify POPF-related factors. Especially the consistency of the pancreas, the diameter of the duct, and the anastomosis technique have been considered the subject of study[8,9]. The current study is critical because we examined the risk of POPF from a clearer perspective (single surgeon, same procedure, two demographically similar groups, and clinicopathologically more homogeneous).

Many studies[4,10,11] show that obesity increases the risk of POPF. As the BMI increases, the pancreatic texture is softer due to the increase in the fat ratio in the pancreatic tissue. However, the risk of POPF development is higher in patients with soft pancreatic texture[11]. In our study, it was seen that increasing BMI increased the formation of pancreatic fistula, which was in line with the literature. On the other hand, the fact that the POPF rate does not increase in patients in whom perioperative pancreatic texture is evaluated as soft creates a contradiction in itself since the manual perioperative evaluation of density is not based on objective criteria. POPF is associated with increased BMI, and this should be considered a more reliable result.

Many studies[12,13] have shown that POPF development rates are independently higher in patients with a pancreatic duct diameter smaller than 3 mm. However, there was no statistically significant difference between pancreatic duct diameter and POPF in our patient group. Increasing the diameter of the pancreas allows for a relatively more straightforward pancreatico-enteric anastomosis. However, during the procedure, the surgeon's use of a visualization-enhancing (surgical loupes, etc.) inventory and his previous experience in microsurgery allows him to perform a safe anastomosis to smaller pancreatic ducts.

Perioperative nutritional status is an essential factor closely related to postoperative surgical outcomes[14]. PNI was first described by Onodera et al[15] and was recommended as an indicator of surgical complications and mortality. PNI is calculated using the serum albumin level and the peripheral total lymphocyte count. The PNI was originally used to evaluate perioperative nutritional conditions and postoperative complications in cancer patients. Albumin is a negative acute-phase reactant synthesized by the liver. In the presence of inflammation, albumin levels decrease. Hypoalbuminemia is associated with poor tissue healing, decreased collagen synthesis in anastomoses, and impaired cell-mediated immunity[16]. In addition, peripheral total lymphocyte count reflects the nutritional status, inflammation, and immunity. Therefore, PNI reflects the secondary systemic response of patients to inflammation, nutritional status, and immunity[17]. It has been reported[18,19] that low perioperative PNI affects the complication rate after pancreaticoduodenectomy, including POPF. Previous studies[20] have demonstrated the usefulness of perioperative PNI in predicting complications after pancreaticoduodenectomy, including POPF. In our study group, no relationship was found between PNI and POPF. The PNI score of the patients who developed fistula was not statistically different from those who did not.

It is known[21] that preoperative bilirubin level has a negative effect on long-term outcomes after PD. The effect of bilirubin levels on POPF has also been studied in recent years. Nong et al[22] have claimed that an elevation in the total bilirubin level above 17 g/dl increases the risk of POPF, while in the study conducted by van Der Gaag et al[23], the cut-off value was stated as 15 g/dl. However, there are also studies in the literature that argue against these claims[24]. In our study group, there was no difference between the preoperative bilirubin values of patients with and without POPF. Another controversial issue in patients with preoperative hyperbilirubinemia is preoperative biliary drainage (PBD). Due to the paucity of randomized controlled trials on hyperbilirubinemia and PBD, we can only rely on retrospective data and meta-analyses. However, recent review articles and meta-analyses on this topic have also yielded conflicting results. For example, Moole et al[25] concluded that PBD reduced morbidity after PD, while Lai et al[26] argued that it had no beneficial effect on periampullary tumors. Chen et al[27] specifically addressed the relationship between POPF, an essential factor affecting the postoperative course, and preoperative bilirubin level. Most other meta-analyses[28,29] failed to shed light on this issue. The possible reason for the conflicting results in these meta-analyses is the heterogeneous patient cohorts formed by the inclusion of proxi-

mal and distal bile duct malignancies, endoscopic and percutaneous biliary drainage, bypass, and palliative resections.

The relationship between the amount of intraoperative bleeding and the need for transfusion and POPF has been studied by many researchers[30]. The difference between blood loss and intraoperative blood transfusion is associated with rapid volume loss causing ischemia and tissue edema and may directly affect the healing of the pancreatic duct-mucosa anastomosis. Consistent with the literature[31,32], in our study group, increased intraoperative blood loss increased the risk of POPF development.

DFA levels are a predictor of POPF[33-35]. In our study, DFA value and blood amylase value more than three times were accepted as significant and predictive for POPF. Bassi et al[36] showed that early drain removal (POD 3) was associated with a lower rate of postoperative complications compared to late drain removal (POD 5 or beyond). Early removal of the drain is one of the methods that can be used to reduce complications in patients with a low risk of developing POPF after pancreatoduodenectomy[37]. Having the drain fluid amylase level within normal limits may facilitate the selective removal of drains in patients at low risk of developing POPF, given its high negative predictive value.

This study has several strengths, including the following: patients were operated on by a single surgical team using a standard procedure, thus eliminating the bias that permeates heterogeneous studies. Furthermore, only adenocarcinomas obstructing the lower common bile duct were explicitly selected, thus eliminating the bias that may be brought about by different pathologies known to affect POPF, such as underlying chronic pancreatitis and intraductal papillary mucinous neoplasm (IPMN), neuroendocrine tumors, and cystic neoplasms.

Limitations

There are several limitations to consider when interpreting the results of the present study. As with all retrospective studies, selection bias was a possibility. For example, patients considered to be at very high risk may not be offered surgery. Pancreatic tissue is subjective depending on whether it is classified as hard or soft depending on the evaluation of the surgeon operating. It should not be ignored that there may be a potential bias in the variation caused by the anesthetists responsible for perioperative fluid management and intensive care. The relatively low number of patients also requires working with multicentric and large patient groups.

Conclusions

Despite the limitations, this study makes strong recommendations to reduce the risk of POPF after PD and to make an early diagnosis. POPF risk is increased by elevated BMI and excessive perioperative blood loss. In addition, the diameter of the pancreatic duct can be considered a risk factor associated with the surgeon's experience. DFA level is an easily applicable method that provides early diagnosis for POPF.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethics Approval

The Ethics Committee of Health Science University Tepecik Research and Training Hospital approved the protocol of this study (approval number: 2019-089).

Informed Consent

Since the study was retrospective, patient consent was not required.

Availability of Data and Materials

The datasets used and/or analyzed during current study are avaible from the corresponding author on reasonable request.

Authors' Contribution

S.A., I.S., and A.D.: conceptualization, methodology, software. S.A. and G.O.: data curation, original draft preparation. T.E. and H.E.: visualization, investigation. G.O. and I.S.: supervision. T.E., H.E.: software, validation. S.A., A.D. and G.O.: writing, reviewing, editing.

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