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PROSPECTIVE STUDY

Drain amylase value as an early predictor of pancreatic fistula after cephalic duodenopancreatectomy

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Abstract

AIM: To determine predictors of clinically relevant pancreatic fistulas (CRPF) by measuring drain fluid amylase (DFA) in the early postoperative period.

METHODS: This prospective clinical study included 382 patients with periampullary tumors that were surgically resected at our department between March 2005 and October 2012. A cephalic duodenopancreatectomy (DP) was performed on all patients. Two closed suction drains were placed at the end of the surgery. The highest postoperative DFA value was recorded and analyzed during the first three postoperative days and on subsequent days if the drains were kept longer. Pancreatic fistula (PF) was classified according to the International Study Group of Pancreatic Fistula (ISGPF) criteria. Postoperative complications were defined according to the Dindo-Clavien classification. All data were statistically analyzed. The optimal thresholds of DFA levels on the first, second and third postoperative days were estimated by constructing receiver operating curves, generated by calculating the sensitivities and specificities of the DFA levels. The DFA level limits were used to differentiate between the group without PF and the groups with biochemical pancreatic fistula (BPF) and CRPF.

RESULTS: Pylorus-preserving duodenopancreatectomy was performed on 289 (75.6%) patients, while the remaining patients underwent a classic Whipple procedure (CW). The total incidence of PF was 37.7% (grade A 22.8%, grade B 11.0% and grade C 3.9%). Soft pancreatic texture (SPT) was present in 58.3% of patients who developed PF. Mortality was 4.2%. The median DFA value on the first postoperative day (DFA1) in patients who developed PF was 4520 U/L (range 350-99000 U/L) for grade A fistula (BPF) with a SPT and a diameter of the main pancreatic duct (MPD) of $\leqslant$ 3 mm. For grade B/C (CRPF), the median DFA1 value was 8501 U/L (range 377-92060 U/L) with a SPT and MPD of $\leqslant$ 3 mm. These values were significantly higher when compared to the patients who did not have PF (122; range 5-37875 U/L). The upper limit of DFA values for the first 3 postoperative days in the examined stages of PF were: DFA1 1200 U/L for the BPF and CRPF; DFA3 350 U/L for BPF and DFA3 800 U/L for CRPF. The determined values were highly significant and demonstrated a reliable diagnostic test for both BPF and CRPF.

CONCLUSION: DFA1 $\geqslant$ 1200 U/L is an important pre-

dictive factor for PF of any degree. The trend of DFA3 (decrease of < 50%) compared to DFA1 is a significant factor in the differentiation of CRPF from transient BPF.

Key words: Cephalic duodenopancreatectomy; Periampullary tumors; Pancreatic fistula; Drain fluid amylase level; Prediction

Core tip: The aim of the study is to determine the possibility of early prediction of the occurrence of clinically relevant pancreatic fistula (CRPF) during the postoperative period after cephalic duodenopancreatectomy for periampullary carcinoma by measuring drain fluid amylase (DFA) values during the first 3 postoperative days. Three-hundred and eighty-two surgically treated patients with resectable periampullary tumors were prospectively analyzed between 2005 and 2012. The total incidence of pancreatic fistula was 37.7%. The median DFA values were significantly higher in patients who developed CRPF. We concluded DFA could represent a reliable predictive parameter for CRPF development.

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INTRODUCTION

Pancreatic fistula (PF), especially clinically relevant pancreatic fistula (CRPF), represents one of the most common and serious complications in pancreatic surgery. Early prediction of the PF occurrence is of the utmost importance[1]. If we can reliably exclude the development of CRPF during the early postoperative period (first three days), patients could be treated with a "fast track" protocol, which includes early mobilization, early removal of drains and oral feeding, adequate pain control, a shorter hospital stay and reduced treatment costs[2]. However, if there is a risk of CRPF development, which is accompanied by a higher percentage of life-threatening complications, treatment of patients is more extensive and involves delayed oral feeding and drain removal, possible introduction of somatostatin analogues, antibiotics, and/or interventional radiological procedures.

The incidence of PF in the international literature is variable, from 2%-51% depending on applied criteria[1,3,4]. In 2005, the International Study Group on Pancreatic Fistula (ISGPF) precisely defined pancreatic fistula as the appearance of any measurable volume of drain fluid on or after the 3rd postoperative day with an amylase content 3 times greater than the upper normal serum value[1]. They also proposed a classification scheme upon which the severity of PF was graded precisely according to the clinical procedures and outcomes (grades A, B, and C). Because the biochemical pancreatic fistula (BPF) does not significantly affect the postoperative course, it is very important to differentiate between those patients who will and will not develop PF and also to distinguish the fistula stages (A *vs* B/C). Although it allows for comparison of results between centers, the ISGPF definition of PF is determined largely on the basis of outcomes, making it impossible to determine guidelines for prompt treatment of postoperative PF. One cannot predict the clinical course of patients with verified PF on the third postoperative day based solely on the ISGPF classification[5,6].

There are several risk factors for the occurrence of PF: disease-related (pancreatic texture, pancreatic duct diameter, pathologic diagnosis), patient-related (demographics, co-morbidities, jaundice, neoadjuvant therapy) and intraoperative (surgical technique, type of anastomosis, type of reconstruction, intraoperative blood loss and duration of surgery)[7]. It is crucial to recognize risk factors that can lead to development of CRPF and thus determine further postoperative treatment. The most important factors for pancreatic anastomotic dehiscence are soft pancreatic texture (without marked fibrosis, prone to suture tear) and main pancreatic duct diameter of less than 3 mm.

There are few published studies that analyzed the correlation of drain fluid amylase (DFA) level with the risk of developing PF[8-15]. Even fewer studies analyzed the risk factors for early prediction of postoperative CRPF and its distinction from BPF[13,14,16-20]. The aim of this study was to determine if DFA value can be used as a predictive criterion for the development of CRPF and to distinguish CRPF from BPF in the early postoperative course.

MATERIALS AND METHODS

A prospective clinical study was conducted at our department from March 2005 to October 2012, during which 382 patients with a surgically resectable periampullary tumor were followed. A cephalic duodenopancreatectomy (DP) was performed in all patients. Several patients had been previously treated elsewhere and were referred to our institution for definitive treatment. All surgical procedures were performed by 5 senior surgeons. The surgeon was responsible for choosing the type of surgery [pylorus-preserving DP (PPDP) or classic Whipple procedure (CW)] and the type of anastomosis [pancreaticojejunal (PJ) with duct to mucosa or by invagination, or pancreaticogastric anastomosis (PG) with or without stent placement], because none of these surgical techniques have a statistically proven advantage over the others[21]. We began performing PG anastomosis at our department two years ago, primarily in the patients with a narrow main pancreatic duct (MPD) and soft pancreatic texture (SPT).

In all patients, two closed suction drains were placed at the end of the surgery, one close to the pancreatic

Table 1 Clinical, intraoperative and postoperative characteristics in relation to the occurrence and stage of pancreatic fistula-univariate analysis *n* (%)

Parameter	Pancreatic fistula			*P* value		
	No[1]	BPF[2]	CRPF[3]	P_{12}	P_{13}	P_{23}
Gender (M/F)	137/101	50/37	44/13[1]			
Age	61.1 ± 10.6	60.0 ± 10.4	61.4 ± 8.2	0.518	0.855	0.407
PF	238 (62.3)	87 (22.8)	57 (14.9)	0.011[1]	0.011[1]	0.126
Pancreas texture-soft	9 (10.7)	32 (38.0)	43 (51.2)	0.001[1]	0.001[1]	0.225
MPD diameter ⩽ 3 mm	45 (23.4)	74 (38.5)	73 (38.1)	0.036[1]	0.059	0.910
Soft/MPD ⩽ 3 mm	7/9 (77.8)	31/32 (96.9)	40/43 (93.0)			
Surgical procedure						
PPDP	133 (46.0)	74 (25.6)	82 (28.4)	0.002[1]	0.007[1]	0.653
Whipple	31 (33.6)	35 (38.0)	26 (28.4)	0.739	0.590	0.384
Pathology						
Pancreatic ductal adeno Ca	87 (60.0)	33 (22.8)	25 (17.2)	0.001[1]	0.001[1]	0.169
Papila Vateri Ca	28 (26.9)	35 (33.6)	41 (39.5)	0.493	0.250	0.639
Common bile duct/duodenal Ca	16 (30.8)	21 (40.4)	15 (28.8)	0.444	0.719	0.572
Other						
Blood transfusion (pt's)	147/238(61.8)	46/87 (52.9)	33/57 (57.9)	0.015[1]	0.066	0.610
Blood transfusion (mL)	540.0 ± 345.4	560.7 ± 189.0	504.1 ± 340.4	0.759	0.634	0.416
Hospital stay	14.1 ± 9.0	17.7 ± 6.8	34.1 ± 16.3	0.013[1]	0.001[1]	0.001[1]
Mortality	-	2/87 (2.3)	14/57 (24.6)	-	-	0.001[1]

[1]Significant $P < 0.05$, *n/n*, mean ± SD. MPD: Main pancreatic duct; PPDP: Pylorus-preserving duodenopancreatectomy.

anastomosis and the other near the bilio-enteric anastomosis. Drains were removed if there was no significant drainage (blood, bile, intestinal contents, pus or unusual color raising suspicion of PF), if the DFA values were low, and at the discretion of the surgeon. Somatostatin analogues were predominantly used in patients with "high risk anastomosis" (SPT, narrow MPD). All patients received intravenous antibiotics at the induction of anesthesia and for three days after surgery. Low molecular weight heparin was administered subcutaneously for the duration of hospitalization.

In all patients, we recorded the overall amount of drain secretion and DFA values taken from the drain with higher amylase values during the first three postoperative days or more if the drains were kept longer. The upper limit value for serum amylase in our laboratory is 100 U/L. PF was classified according to ISGPF criteria[1]. Postoperative complications were defined according to the Dindo-Clavien classification[22]. Patients who received a total pancreatectomy because of positive surgical margins, distal pancreatectomy or enucleation of the tumor were not included in the study.

The overall analysis of this study included the following parameters: (1) Preoperative: patient characteristics (age and gender); (2) Intraoperative: type of resection (PPDP or CW), type of reconstruction (PJ or PG), duration of surgery, red blood cell transfusion and texture of the pancreas (hard or soft; estimated during surgery in correlation with postoperative histological finding); and (3) Postoperative: Incidence of postoperative complications and reoperation, histopathological analysis of the resected specimen, type and the degree of tumor differentiation, resectional margin, TNM stage, mortality and hospital stay.

Statistical analysis

Continuous variables were expressed as the mean ± SD or as median (range). Patient characteristics, perioperative and postoperative factors were compared between groups using χ^2 statistics and Student-*t* test. Median DFA levels were compared by means of the non-parametric Mann-Whitney *U* test. The optimal thresholds of DFA levels on the first, second and third postoperative days were estimated by constructing receiver operating curves (ROC), generated by calculating the sensitivities and specificities of the DFA level. These thresholds were used for differentiation between the group without PF and the groups with BPF and CRPF. *P* values less than 0.05 were considered statistically significant. The statistical analysis was performed with the SPSS 16.0 software.

RESULTS

PPDP was performed on 289 of the 382 patients (75.6%), and CW was performed on the remaining 93 patients (PJ 190, PG 16). The median age of the patients was 60 years (range 29-80 years), with a male preponderance (60.5% *vs* 39.5%). The male prevalence was significantly higher in cases of CRPF (Table 1). The majority of patients had a pre-surgical diagnosis of periampullary carcinoma (80.6%). The additional indications for surgery were IPMN, neuroendocrine tumors, chronic pancreatitis, metastatic renal cell carcinoma and melanoma. Median operative time was 394 min (range 240-690 min). The percentage of postoperative complications according to the Dindo-Clavien classification is shown in Table 2.

Overall mortality rate was 4.2% (16 of 382 patients). Causes of death were PF with sepsis (8), bleeding (3), liver failure (2), cardiac (2) and pulmonary embolism

Table 2 Postoperative complications by Dindo-Clavien classification *n* (%)

		Fistula		
		NO	A	B/C
Dindo-clavien	0	201 (84.4)	56 (64.4)	0 (0.0)
	1	15 (6.3)	12 (13.8)	1 (1.8)
	2	8 (3.4)	9 (10.3)	30 (52.6)
	3	10 (4.2)	4 (4.6)	8 (14.0)
	4	4 (1.7)	4 (4.6)	4 (7.0)
	5	-	2 (2.3)	14 (24.6)
Total		238 (100.0)	87 (100.0)	57 (100.0)

Table 3 Drain fluid amylase values on postoperative days 1-3 in relation to the occurrence of pancreatic fistula, pancreatic texture and diameter of main pancreatic duct for patients with pancreatic fistula grade A

Grade A PF				
Postoperative day	No clinical fistula (*n* = 238)	Hard pancreatic texture (*n* = 28)	Soft pancreatic texture diameter ⩽ 3 mm (*n* = 31)	Sig.
1	122 (5-37875)	2097 (116-22039)	4520 (350-99000)	$P = 0.023^1$
	$P = 0.143$	$P = 0.668$	$P = 0.630$	
2	100 (6-1374)	1912 (118-61913)	3347 (397-99000)	$P = 0.108$
	$P = 0.003^1$	$P = 0.133$	$P = 0.001^1$	
3	60 (3- 600)	1130 (200-28020)	1050 (343-90000)	$P = 0.994$

[1]Significant $P < 0.05$, median (range). PF: Pancreatic fistula.

(1). Thirty-three patients returned to the OR (8.6%) for bleeding and sepsis caused by PF, and 8 of these patients died. Positive posterior and/or medial (SMA) surgical margins were present in 37.3% of cases, and 61.3% of patients had positive lymph nodes. In 226 patients (59.1%) intraoperative blood transfusion (hemoglobin < 80 g/L) was required. Intraoperative blood transfusion did not significantly influence the occurrence of any degree of PF (Table 1). There was no statistically significant difference in the amount of postoperative drainage fluid in relation to the occurrence of PF.

PF of any degree occurred in 37.7% of all patients, with no statistically significant difference in occurrence of BPF (22.8%) compared to CRPF (14.9%). Forty-three (51.2%) out of 84 patients with SPT developed CRPF. CRPF was associated more often with adenocarcinoma of the papilla of Vater (39.5%). Patients with SPT had a significantly higher incidence of MPD diameter of ⩽ 3 mm in all PF groups (78%-97%) (Table 1).

The median concentration of DFA exhibited much lower values in the first three postoperative days in patients without postoperative PF (Table 3). Therefore, the data from this group are shown as a control in Tables 3 and 4. Median amylase value (MAV) in the drains on the 1st postoperative day was significantly higher in patients with BPF and the presence of SPT combined with the MPD diameter of ⩽ 3 mm, compared to the patients

Table 4 Drain fluid amylase values on postoperative days 1-3 in relation to the occurrence of pancreatic fistula, pancreatic texture and diameter of main pancreatic duct for patients with pancreatic fistula grade B/C

Grade B/C PF				
Postoperative days	No clinical fistula (*n* = 238)	Hard pancreatic texture (*n* = 18)	Soft pancreatic texture duct diameter ⩽ 3 mm (*n* = 40)	Sig.
1	122 (5-37875)	8250 (117-95000)	8501 (377-92060)	$P = 0.773$
	$P = 0.143$	$P = 0.672$	$P = 0.877$	
2	100 (6-1374)	2990 (367-100000)	9014 (195-100000)	$P = 0.079$
	$P = 0.003^1$	$P = 0.307$	$P = 0.085$	
3	60 (3-600)	2298 (279-100000)	6010 (86-100000)	$P = 0.208$

[1]Significant $P < 0.05$, median (range). PF: Pancreatic fistula.

with hard pancreatic texture (HPT) and any diameter of MPD. MAV on the 2nd and 3rd postoperative day was not significantly different between the same groups. In the patients with BPF and SPT, MAV did not differ significantly on the 1st and 2nd postoperative day, while it was significantly lower on the 3rd postoperative day. The observed trend is similar to the trend seen in the group without postoperative PF (Table 3).

MAV from the drain fluid was also analyzed in the group of patients with postoperative CRPF (Table 4). We observed that the MAV value was similar regardless of the pancreatic texture on the 1st postoperative day. On the 2nd and 3rd postoperative day, MAV was higher in the group with SPT and a MPD diameter of ⩽ 3 mm compared to the HPT group, but the difference was not statistically significant ($P = 0.079$ and $P = 0.208$, respectively). As opposed to SPT, the incidence of CRPF was significantly lower in cases with HPT (18 out of 40). CRPF with SPT and a MPD diameter of ⩽ 3 mm had higher but not statistically significant ($P = 0.877$) MAV on the 2nd postoperative day compared to the 1st postoperative day. There was no significant decrease in MAV on the 3rd postoperative day. We concluded that the persistently higher concentration of DFA without significant decrease until the 3rd postoperative day was the main prognostic value of measuring DFA in patients with CRPF with SPT.

By ROC analysis, we determined the DFA threshold level at each postoperative day for BPF and CRPF with SPT and a MPD diameter of ⩽ 3 mm. As we have previously shown, the presence of SPT, especially in CRPF, was the greatest predictor of the occurrence of PF based on the DFA level on the first three postoperative days. Therefore, all further analysis to determine value thresholds for DFA in the development of these fistulas compared with BPF referred to these conditions. Highly significant values of AUC showed that the given DFA limits for each postoperative day are reliable as diagnostic tests for both BPF (AUC = 0.891-0.990, $P < 0.0001$)

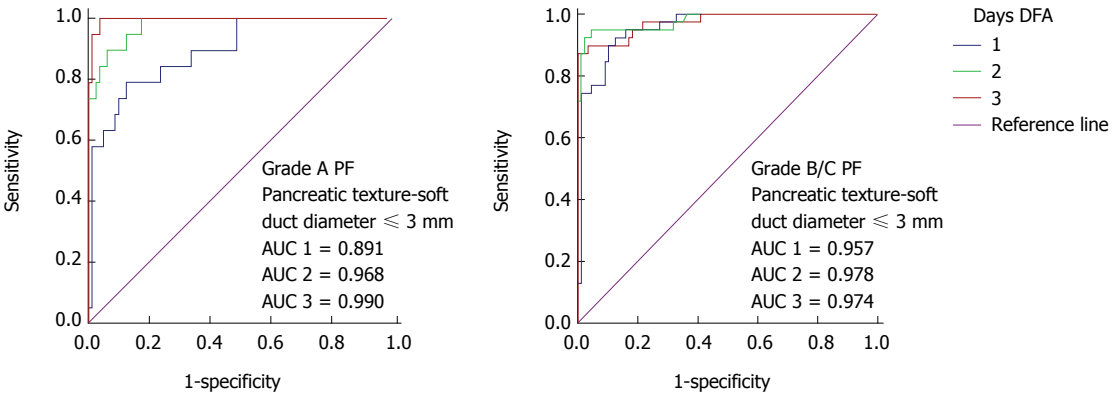

Figure 1 Receiver operating characteristics curve identified a threshold value of drain fluid amylase on postoperative days 1, 2 and 3 to predict biochemical pancreatic fistula *vs* clinically relevant pancreatic fistulas with soft pancreatic texture. PF: Pancreatic fistula; DFA: Drain fluid amylase.

Table 5 Prognostic characteristics of threshold (cut-off) drain fluid amylase levels by postoperative days in the occurrence of biochemical pancreatic fistula and clinically relevant pancreatic fistulas in relation to the texture of the pancreas

Grade PF	Postoperative days	Cut off U/L	Sensitivity	Specificity	FN	FP
A Pancreatic texture-soft, duct diameter ⩽ 3 mm						
	1	> 1200	93.1%	87.5%	6.9%	12.5%
	2	> 800	89.7%	94.3%	10.3%	5.7%
	3	> 350	98.7%	97.8%	1.3%	2.2%
B/C Pancreatic texture-soft duct, diameter ⩽ 3 mm						
	1	> 1200	92.3%	87.5%	7.7%	12.5%
	2	> 1200	89.7%	97.7%	10.3%	2.3%
	3	> 800	90.2%	98.9%	9.8%	1.1%

PF: Pancreatic fistula; FN: False negative; FP: False positive.

and CRPF (AUC = 0.957-0.978, $P < 0.0001$) (Figure 1).

By selecting thresholds with higher sensitivity (89.7%-98.7%), the false negative rate was reduced to 1%-10% with a specificity of 87.5%-98.9%, and the false positive rate was 1%-12%. CRPF developed with DFA1 values below 1200 U/L in only 3 patients. In patients with SPT, the DFA threshold of ⩾ 1200 U/L on the 1st postoperative day did not differ between the compared fistula grades (A *vs* B/C). Lower threshold values of DFA on the 2nd postoperative day in patients with BPF corresponded with the previously analyzed MAV by postoperative days in the case of this fistula type. MAV on the 3rd postoperative day is a diagnostic criterion for predicting the occurrence of CRPF compared to BPF (Table 5). During the development of CRPF, the ratio of DFA concentrations shows only slight day-to-day changes or remains quasi constant (persistent). Thus, in CRPF the marginal threshold values at the 1st and 2nd postoperative days did not differ and were relatively lower on 3rd postoperative day. However, in BPF the threshold DFA values were several times lower on the 3rd postoperative day than on the first day (> 50%).

Values of the defined thresholds overlap, as the threshold of > 800 for BPF is contained within the threshold of > 1200 for CRPF. Therefore, in practical implementation of diagnostic tests that are based on certain threshold values, apart from using threshold values on the first postoperative day, the DFA trend should be followed on a daily basis until the 3rd postoperative day.

DISCUSSION

Pancreatic fluid leakage into the peritoneal cavity in the early postoperative period after DP occurs due to several reasons. It originates either from the pancreatic parenchyma or the MPD (anastomotic leakage). Parenchymal leakage is either from the cut surface of the pancreas (tear through the stitches) or trans-parenchymal, when the pancreas acts as a "sweating" gland that releases an exudate with a high concentration of amylase, similar to pancreatic ascites, seen in patients with acute pancreatitis[10]. The concentration of drain amylase on the first postoperative day could also be affected by the amount of intraoperative leakage of pancreatic fluid into the abdomen. It is often difficult to differentiate between parenchymal and anastomotic leakage, especially in the early postoperative period. Parenchymal leakage is identified by persistently high levels of drain fluid amylase without extravasation of contrast on fistulography and usually stops spontaneously, while the anastomotic leakage shows contrast extravasation at the level of PJ and has no tendency to resolve spontaneously[23-25].

Although consensus has not been reached, measurement of DFA in the early postoperative period after

Figure 2 Incidence of biochemical pancreatic fistula (A) or clinically relevant pancreatic fistulas (B/C) in a soft pancreas depending on the drain fluid amylase values on the first three postoperative days.

DP can be very useful in predicting the development of PF[8,9,10,13,14,16,20,26]. In their study, Molinari *et al*[8] defined a DFA threshold value of ⩾ 5000 U/L as the only significant predictive factor for PF of any grade, with a sensitivity of 92.6% and a specificity of 83.6%. They assumed that high concentrations of DFA1 were caused either by intraoperative leakage of pancreatic fluid or by early and imperceptible spills at the level of anastomosis, which usually preceded the appearance of CRPF. During a successful postoperative recovery, pancreatic function is reduced until the fifth postoperative day and then slowly begins to recover. Complications developed only in those patients in whom DFA1 was ⩾ 5000 U/L and DFA5 was ⩾ 200 U/L, and these complications were explained as a small area of ischemic necrosis at the anastomotic site on the 5th postoperative day. The study was performed on patients after DP and distal pancreatectomy, which represented heterogeneous groups with regard to the different behavior of PF in the presence of anastomosis with the bowel. They did not explicitly

Table 6 Development of clinically relevant pancreatic fistulas depending on a threshold DFA1 (our results in comparison with different series, molinari, sutcliffe)

DFA U/L	Fistula B/C	No fistula	Σ	Sensitivity	Specificity	Fn	Fp
Molinari							
> 5000	39	2	41	68.4%	99.1%	31.6%	0.9%
⩽ 5000	17	236	254				
Σ	57	238	295				
Sutcliffe							
> 350	54	78	132	94.7%	67.2%	5.3%	32.8%
⩽ 350	3	160	163				
Σ	57	238	295				

DFA: Drain fluid amylase.

discuss grades of PF and therefore did not separately observe BPF and CRPF.

Sutcliffe *et al*[9] defined much lower threshold values of DFA1 (⩾ 350 U/L) as a predictor of PF occurrence. Seventy patients with DP treated with a standardized protocol (homogeneous group) were analyzed. However, they did not analyze BPF and CRPF separately and only nine patients had PF. The data they obtained supported the hypothesis that the PF was due to technical error during PJA, which appears immediately and can be detected on the 1st postoperative day. As we found in our results, this study indicated that the concept of "late fistula" is questionable, given that none of the patients who had normal DFA1 values and in whom the drains were removed on the 5th postoperative day developed PF[27].

Our study indicated that DFA1 had significant value in predicting PF, especially with SPT. The established threshold value of ⩾ 1200U/L based on ROC analysis confidently predicts the development of any type of PF (sensitivity 92.3%-93.1%, specificity 87.5%). Significantly higher median DFA1 concentrations were measured in patients with PF compared to those without PF. We noticed that in the group of patients with BPF, DFA3 had the same trend of significant decline as the group of patients without PF. These results differ significantly from the group of patients with CRPF, in which the decline of DFA3 is only moderate (< 50%) (Figure 2).

Our results were analyzed using the threshold DFA1 values defined in the works of Molinari and Sutcliffe (Table 6)[8,9]. We noticed a low sensitivity in the case of a DFA1 threshold value of 5000 U/L (68.4% and 31.6% false negatives) and a low specificity for a threshold value of 350 U/L (67.2% and 32.8% false positives). Isolated measurement of DFA in the early postoperative period is not sufficient, but it is very useful for predicting the occurrence of PF and for the differentiation between BPF and CRPF. Few options have been available for early prediction of CRPF thus far. Several authors tried to answer this problem[12,13,17,18,20,26,28,29] using parameters other than DFA values, such as inflammatory (WBC, temperature, albumin level), pre and intraoperative (pancreatic texture, MPD diameter, intraoperative blood transfusion), high risk pathology, *etc*.[30-32]. However, clinical implementation of these parameters is questionable.

Male sex is more often associated with CRPF. Surprisingly, the amount of intraoperative blood transfusion was not significantly different in patients with and without PF. We do not have an explanation for this, and the explanation for the relationship between intraoperative blood transfusion and the occurrence of CRPF is not entirely convincing. The assumption is that blood loss, especially when rapid, leads to ischemia and impaired healing of the PJ anastomosis. Aggressive intraoperative volume replacement can cause tissue edema in the area of anastomosis, which can lead to the occlusion of the MPD or disruption of the stitches[29]. However, the amount of administered blood depends on the preoperative hemoglobin levels, intraoperative blood loss, the operative technique, and post-operative blood losses.

We found a higher percentage of BPF compared to CRPF in our study. Given that BPF does not affect the postoperative course, we may question the ISGPF definition of PF. The high percentage of BPF could be due to strict usage of the ISGPF definition of PF, and therefore a significant number of patients who have had marginal DFA levels on the 3rd postoperative day were classified as BPF (DFA 300-400 U/L). With this in mind, it may be more appropriate to introduce a 5th day of DFA values for the definition of PF[33,34].

Apart from DFA3, the patient's clinical aspect on the 5th postoperative day is of great importance in our opinion. Recovery of pancreatic function, an increase of DFA in CRPF, infection in CRPF (which can be confirmed in drainage fluid only on day 5) and changes in the appearance of drainage fluid in CRPF (sinister fluid) all occur on the 5th postoperative day[35,36]. It is at this time that we may distinguish CRPF from BPF. However, the problem still remains that early differentiation is needed to allow us to determine a strict protocol in the postoperative management of these patients[3,37,38].

In conclusion, our suggestion is that regardless of the consistency of the pancreatic texture (hard or soft), patients with DFA1 values below 1200 U/L, with a significant drop in DFA3 (> 50%) and with the absence of inflammatory reaction (WBC, fever) could be treated with early drain removal on the 3rd postoperative day to avoid the development of late pancreatic fistula.

COMMENTS

Background

Pancreatic fistula is one of the most common and serious complications after cephalic duodenopancreatectomy.

Research frontiers

Early prediction of clinically relevant pancreatic fistula (CRPF) is of the utmost importance because its appearance may be accompanied by a higher percentage of life-threatening complications, delayed oral feeding and drain removal, possible introduction of somatostatin analogues, antibiotics and/or interventional radiological procedures.

Innovations and breakthroughs

The authors studied 382 patients who underwent cephalic duodenopancreatectomy for periampullary tumors. The overall amount of drain secretion and drain fluid amylase (DFA) values were measured from the drain with the higher amylase level during the first three postoperative days or more if the drains were kept longer. The total incidence of pancreatic fistula (PF) was 37.7% (grade A 22.8%, grade B 11.0% and grade C 3.9%). Soft pancreatic texture was present in the majority of patients who developed PF. DFA values on the first postoperative day (DFA1) were significantly higher in the patients who developed PF, and a DFA higher than 1200 U/L was a predictive factor of PF of any degree. The trend of a DFA decline to less than 50% of DFA1 on the third postoperative day was a significant factor in the differentiation of CRPF from transient BPF.

Applications

Reliably excluding the possibility of CRPF development during the early postoperative period after cephalic duodenopancreatectomy enables patient treatment with the "fast track" protocol, which includes early mobilization, early removal of drains and oral feeding, adequate pain control, a shorter hospital stay and reduced treatment costs.

Peer review

The authors evaluated the significance of drain fluid amylase to determine the occurrence of CRPF during the early postoperative period after cephalic duodenopancreatectomy for periampullary carcinoma. They analyzed 387 patients and demonstrated that the total incidence of pancreatic fistula was 37.7%. An accurate statistical analysis demonstrated that drain fluid amylase of $\geqslant$ 1200 U/L is an important predictive factor of pancreatic fistula of any degree.

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