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Treatment of Postoperative Pancreatic Fistula Following Pancreatic Resection

Filip Cecka[1*], Bohumil Jon[1], Vladimír Blaha P[2], Zdenek Subrt[1,3] and Alexander Ferko[1]

[1]*Department of Surgery, Medical Faculty and University Hospital Hradec Králové, Czech Republic*

[2]*Third Department of Internal Medicine, Medical Faculty and University Hospital Hradec Králové, Czech Republic*

[3]*Department of Field Surgery, Military Health Science Faculty Hradec Králové, Defence University Brno, Czech Republic*

[*]**Corresponding author:** Filip Cecka, MD PhD, Department of Surgery, Faculty of Medicine and University Hospital Hradec Králové, Sokolská 581, 500 05 Hradec Králové, Czech Republic, Tel: ++420-737-163931; Fax: ++420-495-832026; E-mail: filip.cecka@seznam.cz

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Abstract

Objective: Pancreatic resection is the only potentially curative modality in patients with carcinoma of the pancreas and periampullary region. Morbidity associated with pancreatic resections remains high with the most common cause of complications being pancreatic fistula (PF). PF occurs not only after pancreatic resections, it can develop after pancreatic trauma and acute or chronic pancreatitis as well. As the PF occurring after pancreatic resection may have different course than in other causes, the management is also different. The aim of this study was to evaluate our own results of pancreatic resections with focus on the treatment of PF.

Methods: Hospital records from patients who underwent pancreatic resection from January 2010 through December 2012 were identified from our prospectively entered pancreatic surgery database. The postoperative management was standardized for all patients. Outputs from all drains were recorded daily. The amylase concentration was measured on postoperative day 3. If the amylase concentration was above three times the normal serum value, the drain was kept in place and the measurement was repeated every other day. Postoperative complications and their treatment were recorded into our database.

Results: During the 3-year period of the study, 78 pancreatic resections were performed. Forty patients had one or more complications. The morbidity rate was 51.2%. The in-hospital mortality was 3.8%. The mean hospital stay for all the patients was 19 days and the hospital stay for patients without any complication was 12 days. Twenty-eight patients (35.9%) had pancreatic fistula according to the ISGPF definition. The PF therapy was based on the fistula severity and consisted of conservative measures in the majority of cases. Interventions for the treatment of PF included CT-guided drainage of peripancreatic collections or abscesses in 7 cases, angiography with embolization of pseudoaneurysms in 4 cases and reoperations in 4 cases.

Conclusion: Postoperative pancreatic fistula remains a significant concern. In particular, delayed postoperative hemorrhage associated with PF is a serious complication and has a high mortality rate.

Keywords: Pancreaticoduodenectomy; Distal pancreatectomy; Postoperative pancreatic fistula; Postoperative hemorrhage; Postoperative complications; Treatment; Percutaneous drainage

Introduction

Pancreatic resection is the only potentially curative modality in patients with carcinoma of the pancreas and periampullary region. However, the morbidity associated with this procedure remains high [1]. The most common cause of complications is pancreatic fistula (PF), which occurs relatively frequently after pancreatic resections. In general, PF is caused by the leakage of pancreatic juice into the retroperitoneum or abdominal cavity. PF is not a life-threatening condition in most cases; however it prolongs the hospital stay, increases the cost of the treatment and delays adjuvant treatment in malignant disease [2].

PF occurs not only after pancreatic resections, it can develop after pancreatic trauma and acute or chronic pancreatitis as well. As the PF occurring after pancreatic resection may have different course than in other causes, the management is also different.

PF is generally defined as an abnormal connection between the pancreatic duct epithelium and another epithelial surface containing pancreas-derived, enzyme-rich fluid [3]. PF is caused by exocrine secretion from the remnant pancreatic parenchyma, therefore output of a liquid rich in amylase content is considered to be a defining feature of PF [4]. Pancreatic juice is rich in protease, which after activation causes digestion of peripancreatic tissue and its destruction. Additional digestion and destruction of the surrounding tissue may be followed by the development of peripancreatic fluid collections, intra-abdominal or retroperitoneal abscesses, delayed gastric emptying, and postoperative hemorrhage.

The reported incidence of PF after pancreatic resections varies in the surgical literature from 10% to more than 30% [5]. This wide variability is largely due to different definitions of pancreatic fistula [6]. Most of the definitions are based on the volume, duration, and amylase concentrations in perioperatively or postoperatively placed drains. When various definitions of pancreatic fistula are applied to identical groups of patients, the rate of pancreatic fistula can range from 10% to 29% according to the definition which is applied [6].

A new universal definition of pancreatic fistula was published in 2005 [3]. According to the International Study Group on Pancreatic *Fistula* (ISGPF), pancreatic fistula is defined as output via an operatively placed drain (or a subsequently placed percutaneous drain) of any measurable volume of drain fluid on or after postoperative day 3, with an amylase content greater than three times the upper normal serum value [3]. Three grades of pancreatic fistula have been determined according to the clinical severity as A, B, or C (Table 1).

Grade	A	B	C
Clinical condition	Well	Often well	Ill appearing/bad
Specific treatment	No	Yes/no	Yes
US/CT	Negative	Negative/positive	Positive
Persistent drainage (after 3 weeks)	No	Usually yes	Yes
Reoperation	No	No	Yes
Death related to PF	No	No	Possibly yes
Signs of infection	No	Yes	Yes
Sepsis	No	No	Yes
Readmission	No	Yes/no	Yes/no

Table 1: Pancreatic fistula definition according to the ISGPF [3].

Grade A fistula, also called "transient fistula" has no clinical impact. It requires little or no change in the clinical management of the patient. Grade A fistula is not associated with a delay in hospital discharge; however, the patients may be discharged with the drain. The drains are usually removed within 3 weeks. Imaging studies do not reveal worrisome or suspicious peripancreatic collections.

Grade B fistulas are symptomatic and clinically apparent, and they require changes in clinical management or an adjustment to the clinical pathway. The patients are usually supported by enteral or parenteral nutrition, and the peripancreatic drains are usually kept in place or new drains may be inserted. The patients may have abdominal pain, fever, and leukocytosis.

Grade C fistulas are severe and clinically significant, and they require major adjustments in clinical management. Clinical intervention is aggressive; patients are often placed in the intensive care units (ICU) and have enteral or parenteral nutrition, antibiotics, and somatostatin analogues. A CT scan usually shows worrisome peripancreatic fluid collection(s) that require percutaneous drainage. Surgical revision may be indicated.

The aim of this study was to evaluate our own results of pancreatic resections with focus on the treatment of PF following the pancreatic resections.

Material and Methods

Hospital records from patients who underwent pancreatic resection in the Department of Surgery, University Hospital Hradec Králové, Czech Republic, from January 2010 through December 2012 were identified from our prospectively entered pancreatic surgery database.

The surgical technique used in our department has been previously described [7,8]. Briefly, following the pancreaticoduodenectomy, a pancreaticojejuno anastomosis was constructed in a duct-to-mucosa, end-to-side fashion. Ductal stents were never used, and pancreaticogastrostomy was never performed. Open distal pancreatectomy was performed in a uniform fashion. Sharp transection was performed with a blade. If the main pancreatic duct was visible, it was occluded with a stitch; afterwards, the pancreatic remnant was secured with manual sutures. No staplers were used for the transection of the pancreas in the open procedure. In laparoscopic distal pancreatectomy, the transection was performed with a stapler. In open procedures, three drains were routinely placed in the subhepatic region anterior to the pancreaticojejuno anastomosis, in the left subphrenic area, and in the Douglas space. In laparoscopic distal pancreatectomy, one drain was placed in the left subphrenic area. Prophylactic octreotide was given to all of the patients (100 μg every 8 hours) and continued for 5 days.

The postoperative management was standardized for all patients. Outputs from all drains were recorded daily. The drain amylase concentration was measured on postoperative day 3. If the amylase concentration was above three times the normal serum value, the drain was kept in place and the measurement was repeated every other day. In clinically suspicious cases, ultrasound or CT scans were performed to assess peripancreatic fluid collection. Undrained collections were drained with CT guidance. Several patients with longer hospital stays were transferred to the metabolic unit of the Third Department of Internal Medicine in our hospital, where the conservative treatment continued until the condition of the patients improved enough to allow them to be discharged or until they healed completely.

Pancreatic fistula was defined according to the ISGPF as output via operatively or postoperatively placed drains of any measurable volume of drain fluid on or after postoperative day 3, with amylase content greater than three times the upper normal serum value. Three grades of pancreatic fistula were determined according to the clinical severity. The grades were determined only after complete healing of the fistula [3].

All other postoperative complications were assessed according to the grading system proposed by DeOliveira et al. [9]: grade I is any deviation from the normal postoperative course, e.g. wound infection; grade II requires pharmacological treatment; grade III requires

surgical, endoscopic, or radiologic intervention; grade IV means single-organ or multiorgan dysfunction; grade V is the death of the patient.

All of the data were prospectively entered into the pancreatic surgery database. Preoperative parameters included basic patient demographics (age, gender, and comorbidity) and presenting symptoms. Intraoperative parameters included operative time, perioperative complications, and blood loss. Postoperative events and management included incidence and type of complication, ICU stay, total hospital stay, and especially the treatment of the pancreatic fistula, including reoperations, radiological interventions, and readmissions.

Results

We performed 78 pancreatic resections during the 3-year period of the study. The patient characteristics are summarized in Table 2 and the histological findings are summarized in Table 3.

Characteristics	
Age, years (SD)	63.1 (11.6)
Sex, n (%)	Male 35 (45), Female 43 (55)
ASA score, n (%)	
I	8 (10)
II	44 (57)
III	25 (32)
IV	1 (1)
Mean operating time, min (SD)	
Pancreaticoduodenectomy	310 (53)
Distal pancreatectomy	192 (50)
Mean blood loss, ml (SD)	
Pancreaticoduodenectomy	793 (539)
Distal pancreatectomy	580 (439)

Table 2: Characteristics of patients in the study. SD, standard deviation.

Histological findings	**n**	**%**
Pancreatic adenocarcinoma	30	38
Cystic tumor	16	21
Endocrine tumor	9	12
Carcinoma of the papilla of Vater	8	10
Metastatic renal cell carcinoma	4	5
Chronic pancreatitis	3	4
Other	8	10

Table 3: Histological findings of patients in the study.

The mean hospital stay for all the patients was 19 days and the hospital stay for patients without any complication was 12 days. Forty patients had one or more complications, with a morbidity rate of 51.2%. Fifteen patients (19.2%) had complication grade I, 9 patients (11.5%) grade II, 11 patients (14.1%) grade III, and 2 (2.6%) patients grade IV. The in-hospital mortality was 3.8%.

Regarding diagnosis, the most common complications, in addition to pancreatic fistula, were of an infectious nature (15.3%), bleeding (11.5%), delayed gastric emptying (6.4%), cardiopulmonary complications (6.4%), bile leak (2.5%) and neurological complications (2.5%). The most common site of infections was the surgical wound (10.3%).

Twenty-eight patients (35.9%) had pancreatic fistula according to the ISGPF definition and 50 patients had no fistula (64.1%). PF grade A occurred in 11 patients (14.1%), PF grade B in 13 patients (16.7%) and the most significant PF grade C in 4 patients (5.1%). Clinically significant fistulas (grades B and C) occurred in 3 patients (10.7%) after distal pancreatectomy and in 13 patients (26%) after pancreaticoduodenectomy. Although the fistulas that occurred after pancreaticoduodenectomy tended to be more severe, the difference did not reach statistical significance.

PF therapy was based on the fistula severity. Grade A fistulas were treated conservatively. The peroperatively placed drains were kept in place until the drain output diminished or until the amylase concentration was less than three times the upper serum concentration. All the patients stayed in the hospital until the fistula was healed completely.

The fistulas grade B required other treatment modalities. CT-guided drainage of peripancreatic fluid collections or abscesses was necessary in 7 patients. Angiographic intervention due to the hepatic artery pseudoaneurysm was performed in one patient. In the remaining 5 patients, no additional measures were necessary, although the peroperatively placed drains were kept in place to control the fistula. Nine out of 13 patients with grade B fistulas were discharged from hospital even though the fistula had not completely healed. The treatment was continued in the out-patient department. Only three of these patients had to be re-admitted because the fistula treatment did not proceed well. The overall re-admission rate after pancreatic resection in this series was 3.8%.

Four patients had grade C fistulas, and all of them underwent re-operation. Interventional angiography with embolization of a hepatic artery aneurysm was performed in three patients because of severe bleeding. The first patient underwent the first re-operation because of severe bleeding from the pancreatico-jejunal anastomosis; the patient was hemodynamically unstable and thus angiographic intervention was not considered. Hemostasis was achieved during the reoperation but the PF progressed. Completion pancreatectomy was therefore performed at the second reoperation. However, the patient died on the 25th day after the pancreatic resection. The second patient had delayed bleeding which was controlled with embolization of a hepatic artery pseudoaneurysm. However, the bleeding occurred again and this time the angiographic intervention was not successful. Surgical exploration was thus performed as a last resort. It was unsuccessful and the patient died during the surgical procedure - on the 58th day after the primary pancreatectomy. Two other patients underwent reoperation because of septic shock and peritonitis; drainage of the abdominal cavity was performed in both. The condition of one of the patients progressed and he died on the 17th day after the primary pancreatic resection.

The condition of the other one eventually improved and even though other complications occurred in the postoperative period (including bleeding from a hepatic artery pseudoaneurysm which was controlled with embolization), the patient was discharged on the 73rd postoperative day. The overall mortality of Grade C PF in this series was 75%.

In addition to the four patients who underwent reoperation for consequences of PF, three more patients underwent reoperation for early bleeding due to the technical failure during the primary pancreatic resection. Hemostasis in these three patients was achieved during the reoperation and no other interventions were necessary.

Five patients with clinically significant PF (grades B and C) were transferred to the Department of Internal Medicine for further conservative management; their total hospital stay was 58 days on average (range 43 to 73 days).

Discussion

Any deviation in the normal postoperative course of a patient after major pancreatic surgery gives rise to suspicion of the PF development. Clinical signs are usually nonspecific and usually include upper abdominal discomfort, nausea, vomiting, loss of appetite, tender and rigid abdomen, failure to pass stool, dyspnea, tachycardia or other signs of sepsis. Laboratory tests show leukocytosis and increased CRP. A radiological examination is not necessary in routine setting, although it should be performed in suspicious cases. If done in such cases, it reveals fluid collections in the abdominal cavity, pleural effusion, abscesses in the subphrenic areas or retroperitoneum, or a distended bowel [4]. A CT scan often shows unspecific changes such as pancreatic edema or peripancreatic fluid collections. However, late complications such as abscess formation, or visceral artery pseudoaneurysms are clearly visible [4].

The most important diagnostic tool is the evaluation of the effluent from intra-abdominal drains. There can be high fluid output, it can have sinister appearance or the content may be infected [3]. Other complications through which the pancreatic fistula may present include severe wound infection, delayed hemorrhage, or delayed gastric emptying. The index of suspicion is usually higher in patients with several risk factors for developing PF. Amylase concentration of the drain effluent greater than three times the upper limit of normal serum value confirms the diagnosis of PF [3].

The treatment of PF must be individualized according to the clinical condition of the patient. Treatment of Grade A PF is conservative in all cases. The peroperatively placed drains are removed when the drain output diminishes or the amylase concentration is less than three times the upper serum value. No other measures besides keeping the drains in place are necessary [10]. The main issue in these patients is to distinguish temporary PF from the clinically significant PF (grades B and C). The level of amylase in the drain output is of no use, whereas the high level of serum amylase and bilirubin on the day of onset of PF and elevated C-reactive protein over 100g/l predict clinically significant PF [11].

PF grade B requires changes in the management, although the treatment remains conservative. It includes adequate drainage, nutritional support as well as antibiotics. Therapeutic somatostatin or its analogues can be also administered to reduce the pancreatic secretion; however, a recent review and meta-analysis did not find solid evidence for the use of somatostatin analogues in achieving higher closure rate of PF [12]. Percutaneous CT-guided drainage significantly reduces the need for relaparotomy [13] and the postoperative mortality rate [10]. In our series, CT-guided drainage was performed in 7 patients with Grade B PF. Nine out of 13 patients with Grade B PF were discharged home and the treatment continued in the out-patient department. Only three of these patients were re-admitted. The overall re-admission rate in this series was only 3.8%. It is lower than in other series [14]; it is mainly due to fact that the hospital stay in our series is longer. We prefer to discharge the patients only after they are in good condition so that the probability of re-admission is low.

Patients with Grade C PF represent a pitfall in pancreatic surgery. The patients often have sepsis and multi-organ failure. In addition, the mortality rate in this group is very high. Reoperations are often necessary. In the past, completion pancreatectomy was preferred due to the fact that the complete source of necrosis and sepsis could be removed. However, completion pancreatectomy is technically very demanding, requiring splenectomy in most cases, and sometimes even total gastrectomy [15]. Another disadvantage is endocrine insufficiency. Moreover, the mortality of this procedure was inadequately high, reaching up to 100% [11]. Most authors nowadays prefer surgical peripancreatic drainage which is a safer alternative. It is technically less demanding, the endocrine function of the pancreatic parenchyma is maintained and further surgical intervention is not required in most cases [16]. Completion pancreatectomy was performed once in this series with unsatisfactory result. Simple drainage was performed twice and one patient did not survive. Some authors claim that completion pancreatectomy should no longer be considered a method of choice [15].

In distal pancreatectomy the PF is usually less severe, although it can be long-lasting. Several studies have shown that endoscopic stent placement into the main pancreatic duct may resolve refractory grade C PF [17]. We did not have any patients with grade C PF after distal pancreatectomy, and thus we did not consider this treatment option.

Delayed postoperative hemorrhage still represents an important source of concern in patients with PF, and especially PF grade C. It is related to ulceration of anastomosis, leakage of venous anastomosis after portal vein resection, or erosion of peripancreatic vessels. Stepwise destruction of the vessel wall promotes the formation of pseudoaneurysms of the superior mesenteric artery and hepatic artery [18]. Early identification of bleeding sites is difficult due to the lack of specific symptoms. Repeated episodes of intraluminal bleeding or a decrease in hemoglobin are recognized as a “sentinel bleeding”. It may precede major hemorrhage from pseudoaneurysms and thus preventive measures must be taken. Contrast enhanced CT scan followed by interventional angiography provides accurate diagnosis and treatment in most cases [18]. Postpancreatectomy hemorrhage is associated with PF in the majority of the cases. It usually occurs 13 to 27 days after the pancreatic resection. Delayed hemorrhage is not a frequent complication; its incidence is reported to be 3 to 5%. However, it is a severe complication with a mortality rate around 30%.

Delayed hemorrhage is more difficult to manage than early hemorrhage. Important factors which establish the diagnostic and therapeutic algorithms are: 1) time of onset, 2) severity of bleeding, 3) intraluminal or extraluminal manifestation, 4) underlying disease, 5) type of index operation, and 6) possible erosion of vascular structures due to PF [19]. The therapeutic options range from observation, monitoring, and fluid replacement to endoscopy, interventional angiography procedures and relaparotomy. Several suggested

algorithms exist for the treatment of delayed postpancreatectomy hemorrhage [18,19]. In some cases "blind" coiling of the gastroduodenal artery or the first two branches of the superior mesenteric artery can be performed without the site of bleeding being visualized [19]. As surgical access to the bleeding vessel is always difficult due to pancreaticoenteric and bilioenteric anastomosis and the presence of postsurgical adhesions, surgical exploration and hemostasis is recommended as a last resort if previous methods of hemostasis have failed. The surgical procedure can encompass the following options: completion pancreatectomy, vascular reconstruction of the hepatic artery or superior mesenteric artery, and/or suture ligation of the bleeding site [18,19].

In our series, delayed postoperative hemorrhage occurred in four patients, all of them had clinically significant PF; two patients succumbed to their condition (mortality rate 50%).

Conclusions

Pancreatic fistula is a common complication after pancreatic resections. This complication is not life-threatening in most cases but it prolongs the hospital stay, increases the cost of the treatment and delays adjuvant treatment in malignant disease. PF therapy consists of conservative measures in the majority of cases. Reoperation is advocated only in the most severe cases of PF and, if reoperation must be performed, simple surgical peripancreatic drainage is preferred over completion pancreatectomy.

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References

1. Cecka F, Jon B, Dvorak J, Repak R, Subrt Z, et al. (2012) [Palliative surgical treatment of tumors of pancreas and periampullary region]. Klin Onkol 25: 117-123.
2. Pratt WB, Maithel SK, Vanounou T, Huang ZS, Callery MP, et al. (2007) Clinical and economic validation of the International Study Group of Pancreatic Fistula (ISGPF) classification scheme. Ann Surg 245: 443-451.
3. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, et al. (2005) Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 138: 8-13.
4. Callery MP, Pratt WB, Vollmer CM Jr (2009) Prevention and management of pancreatic fistula. J Gastrointest Surg 13: 163-173.
5. Shrikhande SV, D'Souza MA (2008) Pancreatic fistula after pancreatectomy: evolving definitions, preventive strategies and modern management. World J Gastroenterol 14: 5789-5796.
6. Bassi C, Butturini G, Molinari E, Mascetta G, Salvia R, et al. (2004) Pancreatic fistula rate after pancreatic resection. The importance of definitions. Dig Surg 21: 54-59.
7. Cecka F, Ferko A, Jon B, Subrt Z (2011) [Laparoscopic pancreatic resections in experimental setting and clinical practice]. Rozhl Chir 90: 194-199.
8. Jon B, Cecka F, Ferko A, Subrt Z (2008) [Our experience with pancreatic resection procedures. Retrospective analysis]. Rozhl Chir 87: 195-199.
9. DeOliveira ML, Winter JM, Schafer M, Cunningham SC, Cameron JL, et al. (2006) Assessment of complications after pancreatic surgery: A novel grading system applied to 633 patients undergoing pancreaticoduodenectomy. Ann Surg 244: 931-937.
10. Kleespies A, Albertsmeier M, Obeidat F, Seeliger H, Jauch KW, et al. (2008) The challenge of pancreatic anastomosis. Langenbecks Arch Surg 393: 459-471.
11. Gebauer F, Kloth K, Tachezy M, Vashist YK, Cataldegirmen G, et al. (2012) Options and limitations in applying the fistula classification by the International Study Group for Pancreatic Fistula. Ann Surg 256: 130-138.
12. Gans SL, van Westreenen HL, Kiewiet JJ, Rauws EA, Gouma DJ, et al. (2012) Systematic review and meta-analysis of somatostatin analogues for the treatment of pancreatic fistula. Br J Surg 99: 754-760.
13. Zink SI, Soloff EV, White RR, Clary BM, Tyler DS, et al. (2009) Pancreaticoduodenectomy: frequency and outcome of post-operative imaging-guided percutaneous drainage. Abdom Imaging 34: 767-771.
14. Ahmad SA, Edwards MJ, Sutton JM, Grewal SS, Hanseman DJ, et al. (2012) Factors influencing readmission after pancreaticoduodenectomy: a multi-institutional study of 1302 patients. Ann Surg 256: 529-537.
15. Büchler MW, Wagner M, Schmied BM, Uhl W, Friess H, et al. (2003) Changes in morbidity after pancreatic resection: toward the end of completion pancreatectomy. Arch Surg 138: 1310-1314.
16. Haddad LB, Scatton O, Randone B, Andraus W, Massault PP, et al. (2009) Pancreatic fistula after pancreaticoduodenectomy: the conservative treatment of choice. HPB (Oxford) 11: 203-209.
17. Grobmyer SR, Hunt DL, Forsmark CE, Draganov PV, Behrns KE, et al. (2009) Pancreatic stent placement is associated with resolution of refractory grade C pancreatic fistula after left-sided pancreatectomy. Am Surg 75: 654-657.
18. Roulin D, Cerantola Y, Demartines N, Schäfer M (2011) Systematic review of delayed postoperative hemorrhage after pancreatic resection. J Gastrointest Surg 15: 1055-1062.
19. Yekebas EF, Wolfram L, Cataldegirmen G, Habermann CR, Bogoevski D, et al. (2007) Postpancreatectomy hemorrhage: diagnosis and treatment: an analysis in 1669 consecutive pancreatic resections. Ann Surg 246: 269-280.