Postoperative pancreatic fistula after pancreatic resection

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ABSTRACT
BACKGROUND: The failure of pancreatic anastomosis after the proximal pancreaticoduodenectomy (PD) and the failure of pancreatic stump after the distal pancreatectomy with a resulting postoperative pancreatic fistula remain the most feared complications after pancreatic resection. Surgeons have been trying to find a reliable reconstructive technique of pancreatic anastomosis for decades.

METHODS: A literature search was performed to January 2020. Studies giving a detailed description of the pancreatic anastomosis after open PD and pancreatic stump closure techniques after the distal pancreatectomy were included. The aim of this study was review reported data derived from meta-analyses concerning the incidence of POPF according to the International Study Group of Pancreatic Surgery. A comparison of various surgical techniques and their impact on POPF incidence was made.

RESULTS: In the group of clinically relevant POPF (CR- POPF), a well established difference between the patients undergoing POPF-associated interventional drainage or reoperation was observed. Meta-analyses showed that the patients with CR- POPF were statistically more likely to have a small duct size, soft gland texture, particular pancreatic neoplasms and an excessive intraoperative blood loss.

CONCLUSION: Grade C POPF following PD, although uncommon, occurs with a definitive mortality. According to the results of various meta-analyses, pancreatectogastrostomy and pancreatectojejunostomy seemed to be comparable anastomotic techniques following PD (Ref. 54). Text in PDF www.elis.sk

KEY WORDS: pancreatic fistula, pancreaticoduodenectomy, distal pancreatectomy.

Update of definition and grading of POPF

The International Study Group of Pancreatic Fistula (ISGPF) developed in 2005 a definition of postoperative pancreatic fistula. Since its definition, it has reached a global acceptance. Numerous articles validated the ISGPF definition and grading of POPF. While the mortality rates following a pancreatic surgery have come down to less than 5 %, the morbidity still remains high, ranging between 30–50 %, even in the high volume centres (1). Pancreatic fistulas are among the most common complications after PD occurring in 18 % of patients (2).

A decreased rate of complications can be attributable to concentration in high volume, specialized HPB centres, innovation of surgical techniques and perioperative management.

Requirements for an update of the definition and grading of POPF have become imperative, and as the result, the update of the International Study Group definition and grading of POPF was published in 2016, 11 years after an original definition 2005 (3)

The consequences of POPF following a pancreatic resection belong to either “clinically relevant” fistulas „grades B–C“ or „harmless“ grade A fistula” or „no fistula“ at all. According to the updated definition, as a POPF should be defined only clinically relevant condition. In the case of an increased amylase activity found in the fluid from an operatively placed drain without impact on the clinical outcome, no fistula should be reported. POPF „grade A“ by original definition from 2005 is nowadays no longer considered a true pancreatic fistula. It was replaced by the term “biochemical fistula” or „biochemical leak“ (BL) in literature. This BL has no impact on postoperative clinical course (3). On the contrary, a clinically significant POPF grade B and C requires an intensive management and surgical intervention, and percutaneous or endoscopic interventional drainage (ID) is often warranted.

In recent years, an interventional drainage (ID) has become the standard of care for symptomatic postoperative fluid collections. However it is not always evident whether POPF refers to grade B or C. Heidelberg group analysed the cohort of 2,955 patients, in which 403 patients developed POPF (13.6 %), 11 % were grade A, 17 % grade B and 72 % grade C. These patients underwent either ID or reoperation. There was a significant difference between these two groups concerning the hospital stay (33 days vs 47 days) and POPF-associated mortality (0 % vs 37 %, p < 0.0001). According to their results, it was proposed to assign all the patients undergoing ID as POPF grade B and the patients requiring a reoperation should definitely remain within the category grade C (4). Similarly, in a situation when a grade B POPF leads to organ failure or to clinical instability or life-threatening haemorrhage requiring an ICU...
stay with an interventional endoscopic stenting or embolization fistula is considered as the grade C. The largest global study of “grade C” POPFs following pancreaticoduodenectomy analysed 4.301 patients worldwide. In the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP), preoperative and intraoperative variables were compared between the grade C POPFs and non-grade C POPFs. Grade C POPFs developed in 79 patients (1.8 %) (5).

Concerning the fact, that POPF possesses a risk of mortality, many studies made effort to identify risk factors and early predictors for clinically relevant POPF (CR-POPF). Multicentre study carried out by the Japanese Society of Hepato-Biliary-Pancreatic Surgery evaluated the predictive factors associated with a clinically relevant pancreatic fistula grade B/C. Male gender, intraoperative bleeding > 1.000 ml, soft pancreas and drain amylase level on POD 1 of more than 4.000 IU/L were the significant predictive factors for CR-POPF. It seems very important to be able to predict whether the patient will develop CR-POPF in the early period after PD, since these fistulas require changes in patient management and are associated with a higher mortality rate (6). Conversely, the authors of number of other studies reported that amylase and are associated with a higher mortality rate (6). Conversely, whether the patient will develop CR-POPF in the early period after PD, since these fistulas require changes in patient management and are associated with a higher mortality rate (6).

Interestingly, there was the pattern of pancreatic fistula defined by Pratt et al termed as a latent pancreatic fistula defined as initially lacking amylase-rich fluid, but ultimately becoming CR-POPF (9).

As determined by the number of multivariate analyses, the patients with CR-POPF were statistically more likely to have a small duct size, soft gland texture, pathology including ampullary, duodenal, cystic or islet cell neoplasms and an excessive intraoperative blood loss (10, 11). Grade C POPF, although infrequent and accounting for 15 % of all POPF, represents a serious threat to the patient. Its overall incidence of 2.6 % was reported in the patients undergoing Whipple procedures. Development of the grade C fistula may lead to death with a reported mortality rate up to 39 % (12).

Moreover, the importance of CR-POPF lies in the fact that in addition to being a life-threatening complication, it prolongs hospitalization and increases hospital costs.

Most POPF can be managed non-operatively, but a significant number of grade C POPF do require a surgical intervention. The management of pancreatic fistula in the early period after PD is not sufficiently standardized. Surgical options include a peripancreatic drainage with a possible attempt of repair of the site of leakage, construction of a new pancreatic anastomosis, resection of the anastomosis with a remnant ligation, and a complete pancreaticectomy (13).

**Comparison of stump closure techniques**

Generally, there are two widely used methods to accomplish pancreaticojunostomy after pancreaticoduodenectomy: the invagination pancreaticojunostomy or duct-to-mucosa pancreaticojunostomy.

Several randomized controlled trials have been published in order to find out the best reconstruction method for PD. These high volume centres trials compared the invagination to duct-to-mucosa anastomosis or pancreaticogastrostomy to pancreaticojunostomy (10–16). However, we have not obtained a clear consensus as to which reconstruction method is the best for pancreatic-enteric anastomosis. Reported data of POPF rates were 4–18 % in duct-to-mucosa anastomosis, 3–15 % in invagination, 8–25 % in pancreaticogastrostomy and 11–34 % in pancreaticojunostomy (14, 15).

The comparative studies of reliability of pancreaticojunostomosis versus pancreaticogastroanastomosis found often discrepant results, but the recent systematic review and meta-analysis of randomized control trials showed no differences in the outcomes irrespective of the method of pancreatic anastomosis after PD (16). Discrepancies among the studies could result from many factors, as the type of pancreatic anastomosis or the use of pancreatic duct stent are currently not standardized across institutions. Also, an intraoperative drain placement varies according to institutions or consists at surgeon’s discretion. Therefore, further investigations will be necessary to prospectively validate these predictive risk factors to confirm the possible relationship between these factors and the development of CR-POPF. The incidence of spontaneous resolution or response to medical treatment of various forms of pancreatic fistulas (high or low output fistula, pure or mixed fistula, end or side fistula) are different and often quite unpredictable. POPF commonly occurs following either PD or distal pancreatectomy (DP). The prevalence of POPF after a distal pancreatectomy in high-volume centres reaches approximately 30 %. The largest meta-analysis of all the major stump closure techniques during DP and resulting POPF rates suggests the superiority of stapler, combined stapler and suture closure, anastomosis of the pancreatic stump into the jejunum or stomach, and autologous patch application, when compared to a manual suture closure of the pancreatic stump. Furthermore, there seems to be no impact of laparoscopic versus open DP, spleen-preserving vs. spleen-resecting DP, and of sealants like TachoSil1, fibrin-like glues, or the stapler bio-reinforcement Seamguard1 on PF rates after DP (17). Zhang et al in the meta-analysis of 5.252 patients after DP identified the superiority of the combination of stapler and suture closure over suture closure alone. The use of stapler closure or anastomotic closure for the pancreatic remnant after a distal pancreatectomy significantly reduces POPF rates (18, 19). Neither stapler nor scalpel resection followed by hand-sewn closure of the pancreatic remnant during distal pancreatectomy showed any benefit compared to the other method in the terms of postoperative pancreatic fistula (20).

The reported incidence of POPF after a proximal pancreaticoduodenectomy varies about 5–28 % (21). Most of the large pancreaticoduodenectomy series reported the rates of pancreatic fistula over 10 % (22).

Proximal pancreaticoduodenectomy also incorporates the pancreatico-enteric anastomosis, which is associated with a lower average POPF rates (16 %) vs. approximately 31 % for DP.

The risk factors related to POPF include: pancreatic texture, pancreatic pathology, high pancreatic juice output, pancreatic duct size and biochemical parameters. Numerous studies comparing various techniques of PJ failed to find a significant difference in POPF incidence among them. POPF can be often successfully
treated by non-surgical means. Treatment of POPF is predominantly non-surgical. Endoscopic therapy and percutaneous treatments are important therapeutic modalities. Surgical intervention could be required in selected cases (23).

Generally accepted indications for pancreaticoduodenectomy have expanded to encompass a broad spectrum of periampullary tumours including both malignant and benign lesions, chronic pancreatitis and occasionally, trauma. During the last decade, although the perioperative mortality rate significantly decreased after pancreaticoduodenectomy, the incidence of perioperative morbidity remains still high.

The results of the prospective randomized trial comparing pancreaticogastrostomy with pancreatojejunostomy showed that the overall incidence of pancreatic fistula was 11.7%, and the condition occurred with a similar frequency after pancreatojejunostomy (11.1%) and after pancreaticogastrostomy (12.3%) (24). Numerous reports showed no clear evidence for or against one particular method of pancreaticoenteric anastomosis. The choice of pancreatic anastomotic method is often based on individual experience and adherence to basic principles such as: good exposure and visualization; fine, non-strangulating suture placement to produce a patent, watertight anastomosis and in the preservation of the blood supply (25, 26, 27).

An undrained pancreatic fistula might be the most dangerous, especially, when recognized too late. Dutch Pancreatic Cancer Group performed a large study on the adherence to PRISMA guidelines evaluating the post-operative clinical, biochemical and radiologic variables for an early recognition of clinically relevant postoperative pancreatic fistula. In 37 studies comprising 8701 pancreatic resections (8603 pancreaticoduodenectomies and 612 distal pancreatectomies), clinically relevant POPF occurred in 1532/8701 patients (18%). The early prediction variables for early diagnosis of POPF included an elevated serum and drain amylase, non-serous drain efflux, positive drain culture, elevated temperature, elevated C-Reactive Protein and white blood cell count as well as peripancreatic collections on computed tomography (28).

Since the high rates of incidence of CR-POPF are reported in large centres, their prediction and early recognition is of paramount interest. Lower leukocytes and, particularly, lymphocytes can favour a suspicion of POPF after PD. An elevated CRP on the second postoperative day is considered an early biomarker of PF (29).

Some studies indicated that the incidence of POPF after DP is even higher than that of pancreaticoduodenectomy. In the recent Chinese single-centre retrospective analysis, the albumin difference level on postoperative day 1 was recognized as a new, accessible, objective predictor for POPF and might be helpful for the screening of high-risk patients. The rate of POPF was 15.64% (33/211). This is the first study to identify albumin difference as an independent predictor of POPF after DP (30).

Most of the recent studies confirmed POPF independent risk factors such as: long operation time (more than 480 min), intraoperative blood loss of more than 1000 ml, combined splenectomy, BMI > 25, pancreatic thickness (> 15 mm) (31).

Another retrospective study by Chang et al estimated POPF formation by measuring the thickness and sectional area of pancreas with imaging technology taking into consideration an insufficient stapled closure during clamping (32).

On the other hand, the analysis of 157 patients after the distal pancreatectomy by Sivestri et al concluded that the pancreatic division level did not affect the rate of POPF (33).

Tissue texture of the pancreas and the diameter of the pancreatic duct considered as the risk factors for POPF after the proximal resection seemed not to be so apparent in the patients after the distal one. The abovementioned results can indicate that the mechanism of pancreatic fistula formation after these two resection procedures is different (34).

Lot of biomaterials are currently being used for closing the pancreatic stump like fibrin glue, synthetic gasket assisted reinforced staplers, mesh reinforcement of the staple line, polyglycolic acid (PGA) mesh, etc (35). However,RCT by Kondo et al failed to show any advantages of mesh reinforcement in terms of POPF over a stapled closure without mesh (36).

Although the effect of biological materials on the prevention of POPF remains still controversial, further research on improving the suture technology combined with new materials for the prevention of pancreatic fistula is still reasonable. A detailed instrumental/stapler management like a slow parenchymal flattening technique by Okano et al or prolonged peri-firing compression were described with the aim of avoidance of tearing of the pancreatic parenchyma during transaction (37, 38, 39).

An introduction of laparoscopic distal pancreatectomy revealed an issue of the stapler size selection, however Kim et al found that there is no suitable-sized cartridge for a pancreas thicker than 12 mm (40).

In the patients suitable for body/tail resection, the preoperative endoscopic pancreatic duct stenting was attempted assuming its protective impact on the reduction of POPF incidence (41). In 2017 Heidelberg group completed the prospective clinical trial with an injection of a smooth muscle relaxant into the pancreatic duct before distal resection. The results were promising, authors concluded that this procedure could decrease the incidence of POPF after DP (42).

Once the POPF appears, the goal of treatment is a sufficient drainage. The resulting peritoneal fluid collection caused by pancreatic fistula could be usually effectively drained percutaneously under CT or ultrasound guidance (43). With a sufficient drainage combined with an antibiotic therapy and nutritional support, most patients would recover uneventfully from POPF.

Role of total pancreatectomy

As it was mentioned, various techniques have been developed to deal with the pancreatic stump. Total pancreatectomy (TP) as one of them avoids pancreaticojejunal anastomosis, it can also be considered an extension of oncological radicality in selected pancreatic cancer patients. The high local recurrence rates after Whipple resection and left-sided pancreatectomy could suggest that pancreatic cancer might develop multicentrically in the pancreatic gland, which makes TP an optimal choice.
Widely accepted indications for TP include malignant pancreatic head tumours with the extension into the left part of the pancreas, locally advanced pancreatic head cancer, wide range changes in the pancreatic main duct, recurrent malignancy in the pancreatic remnant, rescue pancreatectomy with POPF in the emergency setting as salvage procedure to control sepsis, multifocal intraductal papillary mucinous neoplasm throughout the gland, multiple metastases of renal cell carcinoma or melanoma with no extra-pancreatic spread, multifocal neuroendocrine tumours including multiple endocrine neoplasia and hereditary pancreatic cancer. Also a chronic pancreatitis in the setting of intractable pain (44).

International consensus guidelines for the management of intraductal papillary mucinous neoplasm (IPMN) recommend a resection for main duct disease with a clearance of all high-grade dysplasia (HGD). The association of the main duct IPMN with an extensive multifocal HGD represents a clear indication for TP (45). Besides „standard” total pancreatectomy, pylorus- and spleen-preserving total pancreatectoduodenectomy (PsSpTPD) with a segmental resection of both splenic vessels has also been attempted in selected patients. We are the witnesses of expanding criteria for total pancreatectomy and it is probable that we will see more total pancreatectomies in future (46).

Pancreatectomy and autologous islet cell transplantation can be used as a salvage procedure in patients, where all other therapies failed. The results would be superior if performed earlier in the course of their disease. It is also a feasible management option for a complex pancreatic trauma in both adults and children (47).

**Conclusion**

There has been an update of The International Study Group of Pancreatic Fistula of definition and grading of POPF eleven years after its original definition. Treatment of POPF remains predominantly non-surgical. Endoscopic therapy and percutaneous radiologic interventions gained an important role among therapeutic modalities. However, in case of feared grade C POPF, reoperation is often necessary, almost in all affected patients being the only curative therapy and thus the treatment of choice (48).

A large number of different pancreatic anastomotic techniques have been applied by pancreatic surgeons globally, trying to minimalize the risk of POPF. The safest technique of the pancreatic stump closure remains an unsolved issue and an effective strategy for POPF prevention is still waiting for its unveiling. Currently used preventive measures directed to reduce POPF rate have been shown to be ineffective. An up-to-date meta-analyses of randomized controlled trials according to the newest 2016 IS- GPS criteria also showed no significant difference in the rate of POPF in the PG group versus the duct-to-mucosa or telescope PJ group. Pancreaticojejunostomy is considered a safe alternative to pancreaticojejunostomy, especially in patients having very thin, non-dilated pancreatic duct and soft pancreas. According to the results of number of meta-analyses, PG and PJ seem to be comparable anastomotic techniques following PD. The detailed analyses of various reconstructive techniques following pancreaticoduodenectomy identified no difference between PJ and PG in the terms of risk of any surgical complication (49, 50, 51).

Many experienced pancreatic surgeons in high-volume centres do consider a total pancreatectomy in selected cases with a high-risk pancreatic anastomosis and other contributing risk factors. In this respect, TP may serve as an alternative to a pancreatic anastomosis in an effort to eliminate sequel of possible POPF. This approach has been proposed recently, even in a conjunction to auto-islet transplantation (52).

A complete removal of the pancreas definitely eliminates the risk of POPF. However, resulting apancrrectomy is associated with severe metabolic consequences. Total pancreatectomy is currently indicated in case of diffuse multicentric premalignant lesions, namely the “main-duct IPMNs” requiring a resection in every patient fit for surgery, when an entire duct is affected. Moreover, it can remove possible “skip lesions” of the main pancreatic duct that could be missed (53).

Another issue represents a salvage completion pancreatectomy for life-threatening POPF that also carries a high risk of postoperative morbidity and mortality. Despite of well-established surgical procedures, new risk factors concerning a construction of pancreatic anastomosis have recently been emerged (54).

However, additional studies are needed to establish the most efficacious anastomotic technique after PD.

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