A Review of Techniques for Closure of the Pancreatic Remnant following Distal Pancreatectomy

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Key Words

Distal pancreatectomy · Left pancreatectomy · Pancreatic remnant · Postoperative pancreatic fistula · Pancreatic fistula · Closure · Coverage

Abstract

The prevalence of pancreatic diseases needing surgical intervention is continuously rising. Distal pancreatectomy is performed in the case of pathologies affecting the left side of the pancreas. More and more sophisticated surgical techniques have appeared and an increasing number of published articles discuss the possibilities for closure of the pancreatic remnant. However, the optimum solution is still under debate, as none of the examined techniques have been proven superior in reducing the incidence of the most common surgical complication, the formation of a postoperative pancreatic fistula (PF). Fistula rates have been stationary at 20–30% in the past decades despite the apparent advancement of medicine. This review presents a survey of the relevant articles examining different closure strategies and risk factors to reduce fistula formation rate. International medical publication database search and assessment was carried out to include the findings of studies investigating the efficacy of pancreatic remnant closure techniques to gain a clearer view on the complexity of pancreas fistulas. Emphasis is on indications for surgery, risk factors for postoperative fistula formation and strategies to seal the pancreatic rem-

nant to avoid leakage. Findings suggest that careful patient selection, meticulous surgical techniques are equally important to reduce fistula rates. Ideal closure of the pancreatic remnant is still to be developed, as none of the widespread techniques (hand-sewn suture or staple closure) proved to be statistically significantly superior. Additional closure and covering methods (seromuscular patch, falciform ligament patch, pancreatico-enteric anastomosis, reinforced staplers, fibrin glue etc.) can have profitable effect but strong evidences are yet to come due to small case numbers. The recent introduction of standardized classification of PFs and future prospective randomized trials are more likely to be susceptible to determine if any of the standard or experimental closure techniques is more beneficial than the others.

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Introduction

Distal pancreatectomy (DP) is the treatment of choice in pancreatic diseases limited to the body and the tail of the pancreas, provided that the head is not involved. Indications for surgery include benign (chronic pancreatitis, pseudocyst, cystadenomas, abdominal trauma) and malignant (pancreas carcinoma, pancreatic metastases, local propagation of nearby tumors) pathologies as well. Recent developments in surgery and advanced perioperative care

led to the reduction of mortality of DP to <2% in most studies. Morbidity, on the contrary, has not changed substantially according to studies available in international literature. The reason behind this phenomenon is the more-or-less constant rate of postoperative pancreatic fistula (POPF) formation. The surface of the pancreatic remnant continues production and excretion of pancreatic juice after the surgery. If the closure is ineffective in terms of sealing the ducts or the remnant surface, the aggressive fluid will lyse the surrounding tissues leading to fistulas, intra-abdominal fluid collections, abscesses or abdominal hemorrhage. Large amount of strategies have been introduced so far to avoid fistula formation, but subsequent analyses have not managed to prove any of the methods superior. This review summarizes the results of recent trials with emphasis on risk factors, cutting and closure techniques of the pancreatic remnant and tries to give an insight on the complexity of dealing with pancreatic fistulas (PFs).

Indications and Method of DP

First documented distal pancreas resection happened 100 years ago by Mayo [1]. The procedure itself was the standard operation for chronic pancreatitis in the 1960s–1970s until more sophisticated radiology imaging and endoscopic retrograde cholangiopancreatography (ERCP) became widely used. Nowadays, indication for DP (or left pancreatectomy) is limited to tumors of the body and tail of the pancreas (adenocarcinoma, neuroendocrine tumors, cystic tumors, intraductal papillary mucinous neoplasms) or malignancies infiltrating the pancreas parenchyma. Rare indication is chronic pancreatitis and pancreas pseudocysts not involving the head of the pancreas. Primary pancreatic tumors count for one-third of resections. Retroperitoneal sarcoma, gastric adenocarcinoma and renal cell carcinoma have an additional one-third share amongst surgical indications, the last third includes rare tumors and benign conditions [2]. A large majority of operations are elective, while 3–16% are emergency distal pancreatic resections following abdominal trauma [3, 4]. In case of verified or suspected malignancy, the procedure is always combined with splenectomy, otherwise the spleen can be preserved if technically feasible. Conventional, open surgery and laparoscopic distal resection are both available. Main steps of the operation are similar in either method: accessing and exploring the lesser sac to determine if the underlying disease is curable with resection, and if so, mobilizing the pancreas left to

the superior mesenteric vein, dissecting the parenchyma of the pancreas and removal of the specimen (20–70% of the pancreas parenchyma) with or without splenectomy.

Definition and Incidence of Pancreatic Fistula

Mortality rates after DP have decreased to 0–3.5% due to improvement in perioperative care and development of more sophisticated surgical techniques. Most publications report <2% DP mortality [4–13]. However, morbidity has not changed significantly. Main complication after dissection of the pancreas parenchyma remains the development of a POPF. Due to the aggressive nature of pancreatic juice, lysis of the surrounding tissues occurs once there is a leakage from the parenchyma or if the pancreatic ducts are not sealed completely.

PF can be internal or external, depending on whether it is communicating with the skin. Postoperative pancreas leakage primarily leads to external fistulas. If the drainage of the surgical site is insufficient or the drain was removed too early then intra-abdominal fluid collections, abscesses, pseudocysts or pancreaticopleural fistulas can develop [14]. Most of these fistulas respond to conservative management, only 10–15% of them require further invasive intervention. The rate of POPF formation is essentially invariant. Different authors have observed a wide variety of fistula rates (4–47%) [12, 15] but it is only partially due to the applied surgical method; publications before 2005 used diverse definitions for PF. Compatibility between these different studies is compromised due to inconclusive and confusing classification for PF (various amylase content, different daily outputs, measured at different days) and non-standardized surgical procedures. Meta-analysis of these trials is either not possible or a large number of – otherwise relevant – papers need to be excluded to reach a comparable study design.

As a response for this problem, a widely accepted consensus definition was developed in 2005 to grade clinically relevant PFs. The International Study Group of Pancreatic Fistula (ISGPF) definition introduced a classification and grading that allows clinicians to use a standardized system to compare pancreas resection results in various centers with regards to complications [16].

Grade A: measurable drain output after postoperative day 3 with an amylase content greater than 3 times the serum amylase activity;

Grade B: fistula leading to hospital readmission, or requiring percutaneous drainage of abdominal fluid or abscess, or causing delayed gastric emptying (i.e., need for

nasogastric tube after postoperative day 7 and/or inability to proceed to regular diet within 10 days after surgery);

Grade C: pancreatic leaks associated with reoperation or death.

While Grade A fistulas are likely to close spontaneously or with conservative management, clinically relevant (Grade B or C) PFs greatly delay recovery after surgery, and thus pose a great burden for the patient and the healthcare system as well. Since POPF formation is considered to be the Achilles heel of pancreatic surgery, a wide variety of techniques have been introduced till date to reduce its rate. As discussed below, DP articles mainly focus on the possibilities to avoid POPF. The primary outcomes of these studies are typically the formation of PF or intra-abdominal fluid/abscess after surgery. Secondary end points are commonly the following: length of hospital stay, surgical site infection rate, wound dehiscence rate, delayed gastric emptying rate, incidence of new onset of diabetes mellitus, quality of life after resection, mortality.

Risk Factors for Fistula Formation

Apart from meticulous surgical techniques and state-of-the-art pancreatic remnant cover methods, studies suggest that appropriate patient selection can as well lead to reduction in POPF risk. Various studies found different independent predictors for fistula formation, but a common aspect is that extensive surgery and the number of comorbidities correlate with PF risk. Uni- and multivariate analyses of registered patient characteristics led to the conclusion that the following factors increase POPF rate [5–7, 11–13, 17–20].

- Male gender;
- Elevated body mass index ($>25 \text{ kg/m}^2$);
- Advanced age;
- Significant comorbidities;
- High American Society of Anesthesiologists score;
- Soft pancreas parenchyma;
- Multi-visceral resections;
- Primary pancreatic malignancy;
- Chronic pancreatitis;
- Intraoperative blood loss $>1,000 \text{ ml}$;
- Operative time $>240 \text{ min}$;
- Decreased albumin levels.

The above list includes characteristics that are independent of the surgical technique. The list does not contain any reference on pharmaceutical agents. Despite the fact that somatostatin analogs (e.g., octreotide) are commonly used

postoperatively, multivariate analysis does not suggest their importance. Although the pharmacologic reduction of pancreatic juice excretion after surgery with octreotide therapy seems logical to avoid leakage and surgical site necrosis, a recent meta-analysis proved no clear evidence that it reduces fistula formation rate at all [21, 22]. Since unequivocal recommendation is not available, decision on the use of somatostatin analogs is left for the preference and experience of the surgeon and the surgical center.

Dissection of the Parenchyma

The left side of the pancreas is resected during distal pancreatectomies while the cut end of the proximal part of the pancreas remains a free surface where functioning parenchyma excretes aggressive pancreatic juice. A variety of strategies have been published to avoid further excretion. While pancreatic remnant closure methods are discussed further below, parenchyma cutting techniques are listed in this section.

Scalpel

Sharp dissection of the parenchyma leaves a smooth surface with intact excreting function. This method has the advantage to easily identify, access and separately ligate the main pancreatic duct (MPD), but always needs additional coverage (e.g., fish-mouth closure, fibrin glue, autologous tissues) to prevent excretion from small ducts to the surrounding tissues.

Linear Stapler

It cuts and simultaneously closes the parenchymal surface and all ducts. It is a quick and widely available method. Advantages and down-sides are discussed in detail in the next chapter.

Ultrasonic Dissection

Suzuki et al. [15] investigated the technique in a randomized clinical trial (RCT) including 58 DP cases. PF rate after ultrasonic dissection of the pancreatic gland was significantly lower (4%) than in the scalpel group (26%) ($p = 0.02$). The authors gave credit to the parenchyma desiccating effect of ultrasonic dissection. In this case, the MPD needs to be ligated separately.

Electrocautery

Transection with electrocautery and consecutive oversewing of the pancreatic remnant led to a POPF rate as low as 4.3% in a retrospective study cohort of 215 patients [23].

Radiofrequency

So far, only limited numbers of porcine and human cases have been reported about radiofrequency ablation (RFA), with emphasis on its advantage to decrease operative time and blood loss with a remarkable reduction in POPF rate. RFA can be an alternative for quick pancreatic dissection and stump closure as well [24–26].

Closure of the Pancreatic Remnant

Database search and review of relevant articles dealing with DP demonstrate a wide spectrum of surgical techniques that have been tested in hope to achieve reduction in POPF rate. The list includes hand-sewn suture of the cut end, linear stapler closure, separate ligation of the MPD, use of absorbable reinforced stapler closure, pancreatocenteric anastomosis, ultrasonic dissection devices, seromuscular patch, fibrin glue sealing, surface active meshes, patching of the pancreatic stump with omental plug or falciform ligament and various combinations of the above. Only a limited number of prospective, randomized trials and meta-analyses are available with no definite statistically significant results, which leads to an ongoing debate to decide if any of the techniques are favorable.

Hand-Sewn Closure

The remnant of the pancreatic stump is cut and closed with 4–0 or 5–0 monofil interrupted single sutures or U-sutures in a ‘fish-mouth’ fashion [19]. Advantage of suturing is its availability and low cost. However, it is time-consuming and technically not feasible on soft, fragile pancreas parenchyma and is challenging laparoscopically [27]. Reported POPF rates have a wide spectrum (9–61%), which is partially due to non-standardized fistula definitions and different, additionally used methods in various studies [17, 30].

Stapler Closure

Linear staplers have the ability to cut and at the same time seal the pancreatic remnant. It is a quick and technically easy method and is available in minimally invasive settings as well. Down-sides are the higher costs and the lack of individual ligation of the MPD. Furthermore, it seems unsafe to use staplers in a pancreas with thick parenchyma [18, 28].

The DISPACT trial was a multicenter prospective RCT of 450 DP cases showing a statistically non-significant trend toward lower fistula rates in the stapler closure

group when compared to the hand-sewn suture group. No difference was noted in secondary end points including wound dehiscence, wound infection, total operating time, intra-abdominal fluid collection, length of hospital stay, new onset of diabetes mellitus and mortality [4].

A meta-analysis of 16 articles, including 671 patients with stapler closure and 1,615 patients with suture closure was published in 2010. No statistically significant differences were noted between the two groups; however, stapler closure group had a lower rate of PF (22.1 vs. 31.2%) and abdominal abscess formation [29]. Another systematic review and meta-analysis of 2 RCTs (evidence level 1b) and 8 observational studies (evidence level 4) including 1,080 patients showed a trend in favor of stapler closure of the pancreatic stump [30]. The latter was published before the acceptance of ISGPF classification, so compatibility of the different studies was a limiting factor.

A number of individual observational studies suggest the validity of the above findings. A retrospective study of 46 patients observed no significant difference in non-absorbable suture or stapler closure of the pancreas, although staple closure had a lower rate of PF formation (19 vs. 11%) [22]. Bassi et al. [31] favored staple closure over hand-sewn sutures in a prospective single-center randomized trial. A Japanese multicenter retrospective analysis of 388 patients observed significantly lower fistula rates in stapler closure patients (POPF 21% in stapler closure group vs. 50.6% in case of non-stapler closure) [9]. Study groups of Takeuchi et al. [32] and Fahy et al. [33] described statistically significant stapler closure superiority in terms of fistula formation (0 vs. 35%; $p = 0.03$).

On the other hand, Kleeff et al. [17] published higher morbidity rate after stapler closure (2b level of evidence) raising the theory that stapling causes focal necrotising pancreatitis in the surrounding of ligated and therefore non-draining pancreatic ducts. Reeh et al. [7] used logistic regression in their study of 283 consecutive DP cases to find significantly higher PF rate after stapler closure. Sheehan et al. [34] observed 14% fistula rate in the suture group compared to 25% in the stapler group (p value unknown).

The above studies agreed that intra-abdominal abscess formation rate is lower in the stapler closure group, but none of them showed statistically significant differences in this context. These combined data suggest a trend to favor stapler closure over hand-sewn suture closure with emphasis on the need for more prospective RCTs and comparable study designs using the standardized ISGPF classification to avoid controversial results.

Separate Ligation of Pancreatic Duct

Studies demonstrated that MPD ligation leads to reduction in PF formation, and its specific ligation is especially important in the case of hand-sewn suture of the pancreatic stump [2, 13, 20, 35]. MPD ligation always needs to be supplemented with an additional parenchyma sealing.

Reinforced Staple Line

A recent meta-analysis compared bare metal staples to reinforced staple loads. Five retrospective and 5 prospective non-randomized observational studies were included. A total of 483 stapled pancreatic resections had an overall fistula rate of 21%. Fifty-two percent of the patients ($n = 249$) had bare metal stapling of the pancreatic stump with a fistula rate of 24% (61 cases). The reinforced staple group (48%, $n = 234$) had a PF rate of 17% (39 cases). These numbers mean a non-significant trend favoring reinforced staple resections. A subgroup analysis of only the prospective studies found that bare staple technique leads to a significantly higher risk of PF when compared to reinforced stapling (RR 14.45, 95% confidence interval (CI) 3.15–66.21 – CI was notably wide). The retrospective data used in the meta-analysis had significant heterogeneity, which is caused by the variability in data collection, patient selection, surgical technique or PF definition.

Prospective data collection is considered to pose stronger clinical evidence than retrospective studies; so, it is indeed a remarkable finding that reinforced stapling is superior to the use of bare staplers in pancreatic stump closure. The authors recommended the use of reinforced staples as preferred technique for closure [36]. Jimenez et al. [37] found significantly lower fistula rate (8 vs. 39%) and thus shorter hospital stay in the reinforced staple group in two consecutive studies when compared to bare stapling [38]. The use of two-row absorbable lactomer staples was found to result in a remarkably low, 0.6% rate of PF in a newly published prospective trial of 150 distal pancreatectomies performed under two decades. Authors reported only 1 Grade B fistula, responding to conservative management in their study. The overall postoperative morbidity was 3.3% with no mortality [39].

Pancreaticoenteric Anastomosis

The MPD is ligated; then a hand-sewn single layer capsule-to-seromuscular pancreaticojejunostomy is performed with non-absorbable sutures and with Roux-en-Y jejunal loop. End-to-end or end-to-side anastomoses have also been published with 0% fistula rate in small observational trials; however, operation time was significantly higher when anastomosis was created. Mortality

rate, length of hospital stay, infection or surgical bleeding rates were not different in the study groups when compared to conventional closure [17, 40]. Another retrospective study showed a POPF reduction to 11% in a cohort of 47 patients with pancreaticoenteral anastomosis, although postoperative hemorrhage was higher in the anastomosis group [41].

Ultrasonic Dissection

The parenchyma desiccating effect of ultrasonic dissection devices has been described in the previous section. It is a quick and easy method but has higher costs and only small numbers of published cases are available to date. When used, selective MPD ligation needs to be performed.

Coverage of the Pancreatic Remnant

Seromuscular Patch (Jejunal Loop or Gastric Serosa)

A randomized, single-center trial found statistically significant reduction in POPF and intra-abdominal fluid collection rate in cases where serosa layer of the first jejunal loop was sutured to the pancreatic remnant. Disadvantage of the technique is longer operation time and higher rate of delayed gastric emptying [17, 42].

Fibrin Glue Sealing

Supposedly once sprayed, fibrin glue prevents leakage of pancreatic juice from incompletely sealed small ducts or from the necrotic edge of the pancreatic stump. Suzuki et al. [43] found that it reduces the formation rate of POPF (from 40 to 15%). According to Ohwada et al. [44], fibrin glue sprayed on the pancreatic remnant before suturing the cut end ('sandwich' technique) leads to fewer PF than being sprayed on the already sutured end (9 vs. 27%, respectively, $p = 0.01$). However, a dual-institution prospective RCT proved no measurable effect of fibrin glue, while causing a mean rise in operation cost by 470 USD per case [45].

Surface Active Meshes

Fibrinogen/thrombin-coated collagen (e.g., TachoSil®) can have additional effect on sealing of the small ducts [17].

Falciform Ligament Patch

A mobilized, pedicled, vascularized falciform ligament patch is used to cover the pancreatic remnant. Iannitti et al. [46] described the technique first in a retro-

spective analysis in 2006 with PF rate of only 5.3%, (although the development of PF was only investigated in the first postoperative week). Walters et al. [47] used similar technique in a small cohort with a POPF rate of 8.7%. This finding was confirmed by a prospective observational study showing significant superiority of autologous (falciform ligament or seromuscular) coverage of the pancreatic remnant when compared to the control group with no additional coverage. Clinically relevant (Grades B and C) fistula rates, hospital stay and treatment costs were equally lower in their experimental group. Vascularized patches have the advantage of using viable, enduring tissue, but it has technical down-sides as well, such as the potential strangulation/compression caused by the ligament 'band' that is drawn from the anterior aspect of the liver to the retroperitoneal area. Use of falciform ligament therefore has been described to lead to an elevated risk of developing delayed gastric emptying [48].

Interesting finding was published by Carter et al. [45] in 2013. Their study group planned a dual-institution prospective RCT using a completely detached falciform ligament piece to cover the pancreatic remnant in their experimental group. Since their autologous patch was not pedicled, compressing effect was avoided, but on the other hand, the cover did not have vascular supply. When compared to the control group (sutured or staple closed patients), they found identical (20–20%) fistula rates. Also, there was no difference in fistula grade incidence, and groups had comparable complication rates and length of hospital stay. Since midterm analysis of data proved no difference between the study groups, this trial was closed before the end of the enrollment process of the statistically required number of patients. An ongoing prospective randomized controlled trial, the DISCOVER study was launched to further evaluate if additional pancreatic stump coverage has clinically relevant importance. Patient enrollment to the study has finished, publication of the results is imminent [48].

Discussion

Pancreas surgery remains one of the most challenging fields amongst abdominal interventions. Technically demanding operations are performed after a complicated access to an otherwise difficultly operable gland. Furthermore, they are associated with a high rate of postoperative complications and a spectrum of diseases with poor prognosis. Approximately 17% of all pancreas resections are

DP; therefore, achieving a safe and reliable method to close the pancreatic remnant would be of great value [17]. The most common postoperative complication, the formation of PF, remains a clinically unsolved problem, as its rate has not changed in over two decades despite the evolution of surgical instruments and improvement of perioperative care. The importance of PFs is overwhelming, as shown by the fact that all the reviewed and quoted publications set their primary study end point to be POPF formation rate.

Pancreas fistula not only poses a devastating impact on quality of life, but greatly delays the commencement of an adjuvant oncologic treatment in case of an underlying malignancy. This effect further reduces the already low survival rate of pancreas cancer leading to even poorer prognosis. Constantly draining pancreas fistula significantly increases length of hospital stay and, once the patient is discharged, it leads to more frequent outpatient visits causing higher healthcare costs [4, 20, 23]. The rate of clinically relevant fistula (Grade B or C) formation has not changed essentially (approximately 20% of distal pancreas resections) in over 20 years despite novel surgical techniques.

However, it is difficult to estimate an exact rate of fistula rate since different authors used different, non-standardized definitions for PF. At least, this was the case before the development of the ISGPF consensus. If any of the 3 criteria of fistula classification (fluid amount, amylase concentration and postoperative day) is altered, then the morbidity rates are not comparable or at least they should be handled with caution. In addition, POPF is a dynamic variant, while some low grade fistulas disappear without intervention, complicated fistula ratio may increase between postoperative days 7 and 30 [4]. Further difficulty in finding out true fistula rates is that clinically irrelevant (Grade A) fistulas were not always reported in recent studies.

In the era of evidence-based medicine, choosing the best available method to close the pancreatic stump should be a matter of well-designed prospective, randomized, double-blind, multicenter studies. However, 1a level trials are probably not going to be available in the near future since blinding of the surgeon is not feasible. On the other hand, blinding of the patient does not seem to be necessary as development of PF is not likely influenced by the patient [48]. Given the publications that are available in international databases (e.g., NCBI National Library of Medicine (PubMed), Embase and the Cochrane Central Register of Controlled Trials (Central)) certain conclusions can be reached.

Pancreas surgery seems to be safer when centralized, for morbidity and mortality rates are both lower in high volume centers. Mortality rates have decreased to an acceptable minimum (below 2% in most publications) in the past decades. Morbidity on the other hand has been stationary lately. The purpose of this review is to enumerate risk factors and technical achievements that can alter clinical outcomes.

Complication rates after DP are dependent on surgical technique and most probably on the surgeon as well [49]. Patient factors are also important, as carefully selected cases will lead to lower chance of surgical failure. Advanced age, male gender, obesity, significant comorbidities, low albumin levels are independent risk factors for fistula formation as well as extensive surgery (multivisceral resections, increased operation time or significant blood loss). The chosen method to dissect the pancreas seems equivocal as long as all the ducts and free parenchyma are sealed. Soft pancreas parenchyma is more difficult to deal with but on the other hand, thick parenchyma is more prone to leak if staplers are used. Otherwise no convincing evidence or guideline exists on whether scalpel dissection, stapling, electrocautery, RFA or ultrasonic dissection is more preferable. Administration of intravenous somatostatin analogues were mentioned as part of the postoperative protocol in a remarkable amount of studies although no clear evidence exists that reduction of pancreas juice excretion alters POPF rate [21].

Closure of the remnant is a much more controversial and confusing area. The long list of available methods reflects the fact that none of the discussed techniques is unquestionably superior to the others. While a few studies prefer hand-sewn closure to avoid POPF, systematic meta-analyses showed a non-significant trend toward stapler closure to be more reliable than sutures [29, 30, 50]. Other comprehensive studies found suture closure and stapler closure to be identical in terms of complications [4, 10, 11]. While pilot studies were optimistic about covering the pancreatic remnant with autologous tissues (omental patch, falciform ligament, gastric wall, jejunal serosa), one prospective trial found no change in POPF ratio, and one prospective randomized trial needed to end halfway before finishing the enrollment process due to lack of difference between the results of the study groups [5, 45]. The findings of DISCOVER trial are yet to be published [48].

Using bioabsorbable reinforced staplers seems to be a promising approach with indisputably low fistula rates, but so far, findings are limited to observational studies only [39]. Selective MDP ligation, fibrin glue, fibrinogen and thrombin-coated collagen or mesh cover are all sec-

ondary methods that are available for additional safety but are likely to have measurable effect only on treatment costs.

A more functional aspect on avoiding fistula formation would be pancreatic duct back pressure reduction. Hashimoto and Traverso [12] found that preoperative endoscopic ablation and/or stenting of Wirsung's duct was a significant risk factor to reduce risk of clinically relevant (Grade B or C) stump leakage (rate as low as 3%). The same study reports a higher rate of PF in patients who received intravenous opioid analgesia due to epidural analgesia failure.

One possible explanation for these findings is the following. The lack of endoscopic intervention of the MPD means intact pancreatic sphincter, while opioid analgesics have a side effect to increase sphincter tone. Both attributions supposedly lead to increased back pressure of the Wirsung's duct, which can facilitate leakage and thus PF development after pancreas resection. The study recommends the use of epidural analgesia over intravenous opioids in the postoperative phase and consideration of pre-operative endoscopic sphincterotomy to reduce PF rate. While on the other hand, endoscopic intervention is not necessarily part of the diagnostic investigations in distal pancreatic diseases and it also has notable morbidity; so routine use of ERCP is not recommended in the work-up process to avoid PF.

Back pressure reduction was also the strategy of Fischer et al. [51]. In an experimental group of 16 patients with DP, a pediatric feeding tube was inserted in the MPD, which was placed 1 cm from the cut end and reached into the duodenum to reduce ductal pressure. Statistically significant reduction in PF rates were observed when compared to the standard stump closure.

The small amount of published cases is a limiting factor in evaluating the usefulness of stenting but it is indeed an interesting topic to lead further investigations on.

Conclusions

Despite the evolving surgical techniques, the rate of PF formation is still high and it remains the main source of complications after DP. Safer perioperative patient care decreased mortality to an acceptable minimum, but clinically relevant fistulas still afflict every fifth patient undergoing surgery, having an impact on quality of life, leading to longer hospital stays, requiring re-interventions and increasing healthcare costs. Effective sealing of the pancreatic remnant is the key to avoid fistula formation.

Widely accepted techniques are hand-sewn sutures and linear stapler closure, with a statistically non-significant trend to favoring the latter method. Observational studies introduced numerous alternatives for dissection of the parenchyma, for closure (main duct ligation, reinforced staplers, pancreatocenteric anastomoses) and for coverage (seromuscular patch, falciform ligament patch, fibrin glue, surface active meshes) of the free pancreatic surface. However, comparison of the results is often misleading due to variable study designs and fistula definitions. The standardized classification of POPF is a great aid for future studies to be more comparable. Since there is no op-

timum standardized surgical technique to date, and the skills of the operating doctors are not a matter of comparison, it is difficult to assess superiority of one closure technique to another. Randomized, prospective, multicenter clinical trials should be carried out to further evaluate if any of the discussed techniques can be advised as standard method.

Disclosure Statement

None.

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