Journal of Surgery
[Jurnalul de Chirurgie]
Review Article Open Access

Minimizing Occurrence of Pancreatic Fistula during Pancreatoduodenectomy (Pd) Procedure: An Update

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Abstract

Background: Pancreatic fistula (PF) is the most widely recognized complication of pancreaticoduodenectomy (PD) with diversely reported occurrence rates. Present review focusses on dissecting the surgical treatment modalities that leads to development of PF.

Methods: A retrospective study with the use of hospital database as cases and controls was carried out. Data were tabulated and subjected to strong statistical analysis and inferences were drawn.

Results: As observed the occurrence of PF did not differ in terms of mean age, sex, surgical timings to the procedure, anastomosis techniques or vascular resection.

Conclusion: The surgical approach for PF is related with a higher mortality and morbidity. There is no preferred method of performing pancreatectomy as any procedure can give rise to same mortality rates and risk of endocrine deficiency. In instances of muddled PF, radiological or surgical conservative treatment is needed and surgically duct to mucosal double layered anastomosis have been successful in reducing the PF rates and its validation is still awaited from the trials.

Keywords

Pancreatoduodenectomy; Duct-to-duct (DTD) Pancreatic fistula; Pancreaticojejunostomy

Introduction

What is PD? Pancreatico-duodenectomy is a surgical term applied to the procedure of removal of various extents of pancreas and duodenum. Although the term itself is incomplete as to the extent of removal of organs as it also encompasses removal of common hepatic, common bile duct and gall bladder as well as shown in (Figure 1). Chiefly this procedure is performed in cases of pancreatic head cancer both as a therapeutic and palliative treatment. It's one of the surgical procedures that demands optimal surgical skills and vigilance as with the success also, the patient can succumb into great deal of morbidity, chiefly pertaining to the digestive system.

Recent literature recommends that many elements impact pancreatic leakage after PD, including sex, age, jaundice, operative time, intraoperative blood loss, pancreaticojejunal anastomotic strategy, surface of the remnant pancreas, pancreatic duct size, utilization of somatostatin, and specialist's experience. Different methodologies have been utilized to diminish the rate of PF including pharmacological controls and refinements and alterations in surgical systems, which are evaluated here. We hope that the findings presented in this article will be informative and help the scholars to be updated with the recent clinical studies conducted as well as what to expect in future findings.

Literature Review

For this review, the PubMed database was searched for articles concerning pancreatic fistula and the surgical procedures employed during PD, published in English before July 2016. We used the search terms "Pancreatic fistula" and "Pancreatico-duodenectomy". Clinical study was considered if they evaluated the association of pancreatic fistula rates the pathogenesis, pathological features, and surgical methods in accordance to author's judgment.

Common methods employed in PD: As depicted in Figure 1, there are chiefly 3 types of surgeries performed in PD. Due to the demand of sophisticated surgical facility and technical skills required, the classical procedure of PD is commonly deployed over the world and in low volume centers.

Complications with PD: From the very start of practice with this procedure, besides non surgery associated complications, various complications have been observed as depicted in (Table I).

Recently the operative mortality after PD has essentially declined to 3 to 5%, while the rate of postoperative morbidity stays high running from 30% to 65%. The absolute most noteworthy reason for morbidity and mortality after PD is the improvement of pancreatic hole and fistula. The leakage rate as per late reports shifts from 0% to 25% contingent upon the definition used [1-3]. Stomach sore and discharge are regular sequelae of pancreatic anastomotic leakage which have frequently been connected with a death rate of at least 40%. Pancreatic fistula (PF) consequently has been one of the real entanglements demoralizing specialists from performing PD.

Pancreatic Fistula- Classification and Grading

There has been varying opinions as to the chief and major complications associated with PD. However if we consider the surgical procedure strictly and focus on the organs involved in the procedure, the occurrence of pancreatic fistula stands tall as compared to the occurrence of wound infection. The latter can be associated with any

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Received February 15, 2017; **Accepted** February 20, 2017; **Published** February 27, 2017

Citation: Mazid MA, Akter GS, Ye ZH, Geng X, Liu F, et al. Minimizing Occurrence of Pancreatic Fistula during Pancreatoduodenectomy (Pd) Procedure: An Update. Journal of Surgery [Jurnalul de chirurgie]. 2017; 13(1): 11-16 DOI: 10.7438/1584-9341-13-1-3

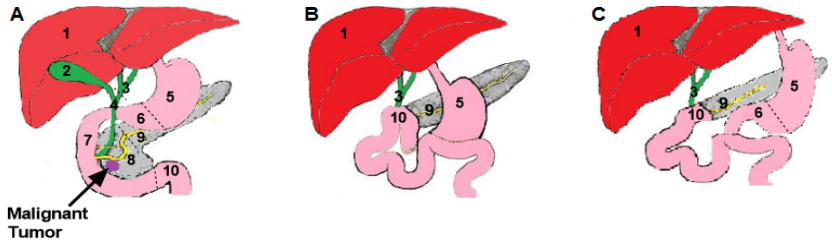

Figure 1: A. Demonstrates anatomical positions of hepato-gastric system with the malignant tumor located in the pancreatic head; B. Demonstrates classical PD with the removal of structures; C. Demonstrates the procedure of pylorus preserving PD.

Table I: Overall complications associated with PD.

Local Complications	Systemic Complications
Pancreatic fistula	Pneumonia
Wound infection	Myocardial infarction
Delayed gastric emptying	Stroke
Intra-abdominal hemorrhage	Death
Intestinal necrosis	
Cholangitis	
Biliary fistula	
Acute necrotizing pancreatitis	
Re-operations	

surgical and most medical conditions while pancreatic fistula occurs only with the procedure of PD.

PF Is defined as an abnormal connection between the pancreas and adjacent or distant organs, structures, or spaces. Historically we can see that in order to define and categorize PF, difference in parameters exists as to the amount of amylase rich pancreatic rich fluid (>10 ml/day, >50 ml/day) as well as in the index time of occurrence (at day 5 or >5 days, at day 11 or for > 11 days) [1-4]. However there has been no consensus in regards to the threshold amount of amylase level as a definition of PF. Similarly the available definitions have been largely based in the daily volume of effluent criteria and the occurrence of fistula development. Adhering to the definitions provided in these studies, the incidence range of PF ranges from 10-29% [1]. To address this, the International Study Group for Pancreatic Fistulas (ISGPF) that comprised of 37 surgeons from various 15 countries compiled, extended and standardized the postoperative PF definition as an external fistula with a drain output of any measurable volume after postoperative day 3 with an amylase level greater than three times the upper limit of the normal serum value. Furthermore, considering the significance of the clinical in hospital course as well as the final outcome, ISGPF also graded the PF into various grades as depicted in (Table II).

We can see that the above criteria consider 9 clinical events. There have been disagreements to theses set 9 criteria by some scholars and some even have attempted to include other intra-abdominal events like peritonitis and hemorrhage that can result due to PF while few others have tried to include consequences of problems that set in with newer anastomotic pathway [1].

Problem Statement and Severity

The outcome of PF is expanded danger of morbidity, mortality, and longer clinic stay and cost. Among the quantity of arrangement as of late distributed, the revealed occurrence of PF taking after pancreaticoduodenectomy extended from 6% to 14% and the announced mortality from 1.4% [1-11]. In addition, likewise, PF is connected with different non fistulous complications, especially delayed gastric purging, ileus, wound contamination, intra-stomach abscess, pancreatitis, discharge, and sepsis. The doctor's facility expenses and rate of reoperation and clinic readmission are essentially increased [3-8]. Table III outlines the risk factors that are associated with PF occurrence. Some of the validations received are also depicted.

Some of unfavorable circumstances for pancreatic fistula development are:

- Intermediate, hard or fibrotic pancreatic tissue
- Pancreatic duct size<3 mm
- Diabetes mellitus and neoadjuvant chemo radiation therapy (decrease in pancreatic exocrine secretion) [1,2].

Since our focus of study was to discuss on the procedures and studies associated with reducing rates of PF, these are discussed in detail.

PF Occurrence According to Resection Type

Central pancreatectomy bears the highest rate of PF formation (20% to 63%) [1] as compared to distal pancreatectomy 5% [1]. One of the studies has also revealed this fact as true where the incidence of PF was 83% for the central and 13% for the distal pancreatectomy while the overall PF occurrence was 16% (Grades A, B, C of ISGPE) in patients undergoing pancreaticoduodenectomy [3]. Moreover, the patients undergoing former procedure also required reoperations and aggressive management in the ICU setting [1,4-7] and had longer hospital stay and required discharge to rehabilitation facilities [12] as compared to distal pancreactomy patients.

Delayed waste of intra-stomach accumulations of over 3 weeks and numerous doctors' facility readmissions (for the most part for image guided percutaneous) are more probable following leaks related after PD [1-8]. The dominating elements connected with the break were expanded weight, higher American Culture of Anesthesiologists score, and blood loss more prominent than 1 L, expanded operation time, diminished albumin level, and sutured conclusion of the stump without the main duct ligation.

A DP with splenectomy was connected with a higher rate of review B or C PF. Significantly ninety-two percent of PF was effectively overseen non operatively [1].

Surgical Modifications in the Anastomosis Technique

Pancreatic duct occlusion

Various techniques either by suture ligation or by application of non-absorbable or re absorbable glue have been applied to occlude the pancreatic duct that is responsible for leakage of pancreatic duct. Some studies have found total occlusion to be effective in terms of lower morbidity [1], decreased mortality and shorter hospital however other studies have demonstrated indifferent results [2] between PJ and ductal occlusion. Moreover the latter studies also revealed a higher rate of PF occurrence.

Table II: Pancreatic fistula grading system based on clinical events as well as the final outcome.

Criteria	No Fistula	Grad A	Grad B	Grad C
		Fistula		
Drain Amylase level	<3 times normal serum amylase	>3 times normal serum amylase	>3 times normal serum amylase	>3 times normal serum amylase
Readmission	No	No	Yes/No	Yes/No
Specific treatment	No	No	Yes/No	Yes
Signs of infection	No	No	Yes	Yes
Death related to fistula	No	No	No	Yes
Sepsis	No	No	No	Yes
Reoperation	No	No	No	Yes
Persistent drainage (>3 weeks)	No	No	Usually Yes	Yes
Clinical conditions	Well	Well	Often Well	Ill appearing
US/CT if obtained	Negative	Negative	Negative/positive	Positive

Source: C. Bassi, C. Dervenis, G. Butturini et al., "International study group on pancreatic fistula definition. Post-operative pancreatic fistula: an international study group (ISGPF) definition," Surgery, vol. 138, no. 1, pp. 8–13, 2005

Table III: Risk factors for PF occurrence.

	Parameters	Predisposition to PF (studies)
Patient related	Age	>70 years old
	Gender	
	Jaundice and Creatinine clearance	Impairment of anastomosis healing
	Coronary artery disease	4 fold increased likelihood
	Malnutrition	
Disease Related	Pancreatic pathology	
	Pancreatic texture	Soft texture has 22.6% more chances of PF and has 10% more chances of having PF
	Pancreatic duct size	Dilated ducts or ducts sixe of >3 mm
	Pancreatic juice output	Increased pancreatic juice
Procedure related	Operative time	
	Imperative blood loss	Blood loss of >1.5 litres
	Resection type	Central vs. Distal pancreatectomy
	Anastomosis technique	
	Surgeons experience	
	Prophylaxis (somatostatin)	

Pancreaticogastrostomy

Diverting the pancreatic remnant into the stomach had been tried by Waugh and Clagett in 1946. This procedure had advantages in terms of elimination of digestive properties of pancreatic juice by the gastric acid and reducing the occurrence of PF. Numerous studies have had supported this fact and as a result this procedure received 3 RCT's, which however failed to demonstrated significant outcome in terms of PF rates, Post-operative complications and mortality [4,13]. Although besides this all the meta analysis done, series published, meta-analysis done have advocated superiority of PG to PD, all of them have suffered publication bias and lack reproducibility in prospective studies [2,3]. Till today both the procedures stand equally efficacious in terms of post-operative outcomes (evidence level 1 and 2).

Pancreaticojejnostomy

This procedure has been practiced for long has been remarkable in reducing the rate of PF formation to 10% (range 2- 19%) [2] during the last 3 decades. PJ is a procedure where the pancreatic stump is connected to the jejunum (that has rich blood supply for healing of the anastomosis and has mobile mesentry). The anastomosis can be performed by direct end to end invagination of the pancreatic remnant with the pancreatic duct into the jejunum or by performing duct- mucosa anastomosis where the pancreatic duct opens into the mucosal surface of the jejunum. The later procedure limits pouring pancreatic juice into the jejunum and theoretically curtails pancreatic juice associated complications. This duct to mucosa procedure is difficult, surgically demanding yet some scholars have opined it to be safer than invagination anastomosis [2,4]. However, some studies have indeed outlined the role of risk factors such as pancreatic texture, size of the pancreatic duct as important in determining the success of duct-to –mucosa technique measured by reduction of PF, RCT performed consecutively revealed indifferent results when duct-to-mucosa was compared with invagination technique.

Isolated roux loop pancreaticojejunostomy

It was also found that the combined anastomosis of PJ and HJ performed in the classical procedure lead to release of bile that helped activate the pancreatic juice and propensity for added digestive damage to anastomosis. With the procedure of isolated Roux Loop, separation of these two anastomosis points was done. Some of the cohort studies demonstrated exciting results of reduction in PF occurrence and mortality, which however received a setback when a following nonrandomized study revealed indifferent results [2]. Thus for now, we can say that isolated Roux loop PG is not associated with lower PF formation (evidence level 3b and 4).

Other Methods

a. Utilization of working magnifying instrument for reproduction: Some have detailed notably decreased rate of PF with the working magnifying lens contrasted with operating loupes [13]. Operating loupes have been utilized by numerous specialists to permit exact recreation of pancreatic anastomosis.

b. Anastomotic site: An idea of vascular watershed in the pancreatic neck and its part in ischemia of the cut surface of pancreatic leftover has been proposed by Strasberg et al. [11] them. In view of this idea, the blood supply at the cut surface of the pancreas is assessed in the methods and if important the pancreas is decreased 1.5 cm to 2 cm to enhance the blood supply (38%).

Table IV: Studies pertaining to PF within the last 5 years. Note: the trials whose chief objective was other than reducing PF occurrence are excluded.

Title	Sponser	Target Status
Ultrasound Elastography for Prediction of Postoperative Pancreatic FistulaNCT02589379	University of Zurich	Diagnostic Recruiting
Does Reinforcement of the Staple Line in Left Pancreatectomy Reduce the Rate of Pancreatic Fistula? NCT02149446	Karolinska University Hospital, Sweden	Suture Recruiting
Does Post Operative Pancreatic Fistula, After Left Sided Resections, Heal Faster After the Introduction of a Pancreatic Stent? NCT02220010	Karolinska University Hospital, Sweden	Stent Recruiting
Predictive Risk Factors for Pancreatic Fistula Grade C After Pancreaticoduodenectomy NCT02322424	Wakayama Medical University, Japan	Risk Factor Recruiting
Different Stapler Cartridge For Pancreatic Stump Texture To Prevent Pancreatic FistulaNCT02790333	Yi-Ping Mou, Zhejiang Provincial People's Hospital, HangZhou, Zhejiang, China, 310014	Suture Recruiting
Route of Nutritional Support for Pancreatic FistulaNCT01755260	National Taiwan University Hospital	Nutrition Recruiting
Pancreaticoduodenectomy With or Without Braun Enteroenterostomy: Comparison of Postoperative Pancreatic Fistula and Delayed Gastric Emptying NCT01481753	Johns Hopkins University	Procedural Recruiting
Prospective Trial Evaluating the Effect of Closed Suction Drainage Versus Straight Drainage After Distal Pancreatectomy NCT02343302	Johns Hopkins University	Drainage Recruiting
An Evaluation of a New Technique Utilizing a Biologic Glue and Tissue Patch to Seal the Cut Edge of the Pancreas Following Removal of the Tail of the Pancreas NCT00889213	Thomas Jefferson University	Procedural Recruiting
One-layer Versus Two-layer Duct-to-mucosa Pancreaticojejunostomy After Pancreaticoduodenectomy NCT02511951	The Second Hospital of Anhui Medical University	Procedural Recruiting
Drains in Pancreatic Surgery (DRAPA) NCT01988519	University Hospital Hradec Kralove	Drainage Recruiting
A Prospective, Multi-center Trial for Reinforced Staple During Distal Pancreatectomy NCT02270554	Wakayama Medical University	Suture Recruiting
External Drainage Versus Internal Drainage of Pancreatic Duct With a Stent After Pancreaticoduodenectomy (EDIDPD) NCT01634971	Tianjin Medical University Cancer Institute and Hospital	Drainage Recruiting
Early Versus Late Drain Removal After Pancreatectomy: A Randomized Prospective TrialNCT02230436	Peking Union Medical College Hospital	Drainage Recruiting
A Randomized Trial of Two Surgical Techniques for Pancreaticojejunostomy in Patients Undergoing Pancreaticoduodenectomy NCT00359320	Thomas Jefferson University	Procedural Recruiting
COMPLETED		
Enteral Nutrition in the Treatment of Pancreatic Fistulas - A Prospective Study NCT01025414	Jagiellonian University, Poland	Enteral nutrition is associated with significantly higher closure rates and shorter time to closure of postoperative pancreatic fistula.[1]
Use of Polyethylene Glycolic Acid or Tachocomb to Prevent Pancreatic Fistula Following Distal Pancreatectomy NCT01550406	Seoul National University Hospital	Study results awaited
Role of Octreotide in Preventing Pancreatic Fistula After Pancreaticoduodenectomy (PD) in Patients With Soft Pancreas, NCT01301222	PVS Memorial Hospital, Kochi, Kerala, India, 682017	Not preventive[2]
Reduced Pancreatic Fistula Rate Following Pancreaticoduodenectomy: Trial on Pancreaticogastrostomy Versus Pancreaticojejunostomy NCT00830778	Baki Topal, Belgium	Results awaited
13 Trial Assessing Roux-en-Y Anastomosis of the Pancreatic Stump to Prevent Pancreatic Fistula Following Distal Pancreatectomy		
Stereotactic Radiation to Decrease Pancreatic Secretions NCT01656486	Carolinas Healthcare System, USA	Results awaited
17 Comparison of Feasibility Between Internal and External Pancreatic Drainage in Pancreaticoduodenectomy		Active
Closed Suction Drainage and Natural Drainage of the Pancreatic Duct in Pancreaticojejunostomy NCT00679952	Seoul National University Hospital	Completed has results
External Pancreatic Duct Stent After Pancreaticoduodenectomy NCT01068886	University Hospital, Angers	Decreases PF rate[3]

Isolated Roux Loop Pancreaticojejunostomy Versus Pancreaticogastrostomy After Pancreaticoduodenectomy NCT01859806	Mansoura University	Both procedures are not associated with lower incidence of post operative PF occurence[4]
Effects of Intraarterial Octreotide on Pancreatic Texture NCT01400100	St. Josef Hospital Bochum	A single blous did not deliver clinically significant pancreatic hardness[5]
Randomized Trial of Early Versus Standard Drainage Removal After Pancreatic Resections NCT00931554	Universita di Verona	Patients with low risk of PF, drain can be removed on POD3, prolong period of drain is associated with higher rates of PO complications with ncreased length of hospital stay and costs.[6]
Comparative Study Between Duct to Mucosa and Invagination Pancreaticojejunostomy After Pancreaticoduodenectomy: (PJ) NCT02142517	Mansoura University	Invagination of PJ is not associated with reduction in PF rates[7]
Randomized Controlled Trial on pancreatic Stent Tube in Pancreaticoduodenectomy NCT00628186	Wakayama Medical University	PF occurrence rate similar in both the procedures[8]
ONGOING:		
39 Sandostatin in the Prevention of Postoperative Complications After Pancreaticoduodenectomy (PD)	Mansoura University	Ongoing
Trial Assessing Roux-en-Y Anastomosis of the Pancreatic Stump to Prevent Pancreatic Fistula Following Distal Pancreatectomy NCT01384617	Wakayama Medical University	Ongoing
Comparison of Feasibility Between Internal and External Pancreatic Drainage in Pancreaticoduodenectomy NCT01023594	Seoul National University Hospital	Ongoing
Source:www.clinicatrials.gov		

c. Removal of pancreas in total: Hence it is no surprise that most studies have reported either worse survival or no survival difference between total pancreatectomy and standard PD [2,3].

d. Stenting of the pancreatic duct: However complications, for example, block of the stent prompting to pancreatic fistula and relocation of the stent are disadvantages with transanastomotic stenting. The quantity of studies on pancreatic stenting is restricted and the outcomes are clashing. However in the nonrandomized think about by Imaizumi et al. with 168 patients, there was no huge contrast in the pancreatic fistula rates between end-to-side pancreaticojejunostomy of ordinary delicate pancreas utilizing stented (inward or outside) technique versus non stented strategies (5.7% vs. 6.7%) [2]. However a few reviews have demonstrated that the inside pancreatic duct stenting did not diminish the recurrence or the seriousness of the postoperative fistulas, between PD with or without an inner pancreatic stent (11.3 vs. 7.6%, respectively) [2].

e. Perioperative somatostatin: The method of reasoning of its utilization taking after PD is that by diminishing the volume of pancreatic emission, the pancreatic fistula rate would be diminished due to which the pancreaticoenteric anastomosis would heal better. Perioperative utilization of somatostatin simple and its useful impacts has been seen in a portion of the reviews directed in Europe and Asia. Notwithstanding, contentions have existed with a portion of the reviews [2-4].

Future Expectations

With these mixed and inconsistent results, numerous preoperative, per-operative and post procedural strategies have gained into clinical trials as depicted in (Table IV). Table IV shows a list of trials that are aimed at reducing PF and depicts the mechanisms manipulated. Among the trials that have been completed and results available, pre-operative interventions as well as post-operative strategies have been significant in reducing the occurrence of PF. Manipulation of surgical methods have not been impressive. Yet newer strategies that focus in the surgical technique, use of modified staples for anastomotic closure and manipulating the drainage system are the studies we hope to yield some critical information in the future.

Conclusion

The treatment offered by pancreatic resection has evolved through times and has proved to be highly effective yet surgically demanding procedure. The complications that arises in the form of PF adds significant morbidity and mortality, thus demands more sophisticated researches. Pancreatic surgeons have spent tremendous efforts in finding out effective strategies to reduce PF rates and sadly it hovers to around 15%.

Thus in light to its occurrence, a vigilance applied to study its important risk factors like, morphological structure, its texture, the status and dimensions of the common bile duct, the surgically critical sites of the tumor (ampullary, duodenal, cystic and islet pathology as well as the amount of blood loss; would surely curtail PF rates. Skills in advanced diagnostic methods in the form of CT and MRI would surely help in identifying these risk factors as well as early detection of complications chiefly PF. Surgically, duct to mucosal double layered anastomosis have been successful in reducing the PF rates and its validation is still awaited from the trials. Similarly, varieties of drainage system and pharmacological interventions have emerged in studies that are yet to be validated. The outcomes of trials are eagerly awaited and the target identified does offer us a strong hope in PF management.

Pancreatic fistula is an iatrogenic process and the resultant morbidity as well as mortality is its sequel. Risk to benefit ratio surpasses the severity of complications, yet a surgical induced and identifiable PF needs to be reduced to negligible rates, and we hope the future researches can deliver such which is still an unmet surgical need.

Conflict of Interest

Authors have no conflict of interests to declare.

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