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What are the Predictors that can Help Identify Safe Removal of Drains Following Pancreatectomy?

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Abstract

Background—The management of a drain after Pancreaticoduodenectomy (PD) and distal pancreatectomy (DP) remains a controversial issue. Our aim in this study was to identify a safe time for drain removal.

Study Design—This is a retrospective study, of a prospective database, of patients who underwent a PD or DP at two tertiary care institutions.

Results—A total of 180 patients underwent PD and DP during the observation period. Seventeen patients developed fistulas (9.4%), with 70.6% (n = 12) developing in soft pancreatic remnants vs. 29.4% (n = 5) in firm pancreatic remnants. Patients with amylase levels greater than 173 U/L on a postoperative day three were 11.46 times more likely to form a fistula compared to those with an amylase level at or below 173 U/L (p < .001).

Conclusion—Fistula formation is associated with pancreas texture, duct size, and drain amylase following PD or DP. Patients with firm pancreatic texture and large ducts are less likely to develop fistulas than those with soft pancreatic texture and small ducts.

Keywords

Distal pancreatectomy; Pancreaticoduodenectomy; drain removal; pancreatic fistula; postoperative complications

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Introduction

Surgical outcomes for pancreaticoduodenectomy (PD) and distal pancreatectomy (DP) have evolved with perioperative mortality occurring in less than 2% of cases at high-volume centers. Postoperative complications remain high occurring between 30% and 50% of the time. (1) One of the most common complications is a postoperative pancreatic fistula (POPF) which can be a devastating complication. Risk factors for developing POPF include underlying pancreatic pathology, texture, duct size and increased intraoperative blood loss. (2,3) Furthermore, these patients have longer hospital days and incur greater hospital costs. (4) The rate of pancreatic fistula following PD is 12.9% and distal pancreatectomy 13.0%. (5) Several studies have questioned whether drains should be routinely placed after surgery. (6–8) A recent meta-analysis of drain amylase levels found that amylase content on the first day after surgery is highly accurate in predicting POPF following major pancreatic resection. (9) Fong et al. and Lee et al. have suggested a middle ground in the drain versus no drain debate. (10,11) Meanwhile, a recent systemic review of the literature found that a conservative approach to drain placement, pending further data, is the routine placement of a drain and early drain removal. (12) Given the multiple studies that have evaluated early drain removal our study aimed to define a safe time for drain removal after PD based on three predictors: pancreatic remnant texture, duct size, and drain amylase levels.

Methods

This study was performed under a human investigational protocol that was approved by the Institutional Review Board of Loyola University Medical Center. Our team conducted a two-center evaluation of patients who underwent PD and DP from 2005–2014. Experienced pancreatic surgeons performed all of the surgical resection. Clinical demographics, pathologic and surgical details were recorded and documented by surgeons involved in each case. Reconstruction of the PD remnant included both PD with pancreaticogastrostomy and pancreaticojejunostomy anastomosis.

All patients undergoing surgery received prophylactic antibiotics. In patients who underwent PD two drains were placed at the end of the case, one to drain the biliary anastomosis and other to drain the pancreatic anastomosis. Each was brought out through a separate incision below the abdominal incision and anchored to the skin. Patients who underwent a DP had a drain placed at the sub diaphragmatic space at the end of the case. All patients received proton pump inhibitors during their postoperative course as prophylaxis for stress ulceration. Patients received octreotide only if they developed a postoperative pancreatic fistula (POPF). Patients who had PD also received erythromycin from postoperative day four until starting a general diet. In patients who had PD, metoclopramide was started on a postoperative day (POD) five. A pancreatic fistula was defined as amylase-rich fluid greater than three times serum amylase and a volume greater than 50 ml. Serum amylase levels were obtained if the drain amylase was consistently high to rule out pancreatitis. However, this was infrequently needed except to satisfy our definition of POPF which was amylase-rich fluid in the drain three times serum amylase levels. A clinically relevant POPF was defined as a pancreatic fistula associated with a hospital stay of greater than 14 days or sepsis with a deep space infection requiring a drain or reoperation.

The primary outcome of this study was postoperative fistula formation. The receiver-operator characteristic (ROC) curve was used to determine the optimal post-operative day (POD) three amylase cut point by calculating the area under the curve. The area under the curve (AUC) using POD3 amylase was 0.82 (95 CI: 0.69 – 0.94) (Figure. 1). POD3 amylase level of 173 U/L was selected to maximize both sensitivity (87%) and specificity (64 %) after analyzing several amylase level cut points. The positive predictive value of this cutoff was only 20%, while the negative predictive value was 98%. (Table. 1).

An exact logistic regression model was then used to estimate the odds of fistula formation as a function of univariable and multivariable patient characteristics and clinical measures. A binomial distribution was specified for the response variable, while logit links were used to estimate the odds ratio for each explanatory variable against a referent. Quasi-complete separation was observed for the model using the variable pancreas texture. Meaning, none of the four patients with a hard pancreas texture formed a fistula. Given the small sample size of patients with a hard pancreas texture ($n = 4$), this level was combined with firm pancreas texture and results were reported as firm/hard v. soft.

With so few POPF observed ($n = 17$), two separate multivariable models were analyzed to avoid overfitting. The first assessed day three amylase score adjusting for duct diameter. The second evaluated day three amylase score after controlling for pancreatic texture. In both instances, the univariable model using only day three amylase score presented the best fit using Akaike's information criterion (AIC). We analyzed the data using SAS/STATA software. An alpha error rate of $p < .05$ was considered statistically significant.

Results

Ninety-eight of the 180 patients who underwent PD ($n = 132$) or DP ($n = 48$) were male (54.4%), and 82 were female (45.6%). The average age of patients was 66 (SD = 13). Seventy-seven patients had soft pancreas texture, 94 had firm pancreas texture, and four had hard pancreas texture. Seventeen patients developed fistulas (9.4%) of these, twelve (70.6%) formed in soft pancreas texture and 15 (88.2%) had a small duct diameter (1–3 mm). Of patients who underwent a distal pancreatectomy 5 (29.4%) developed a fistula. Eleven patients had a grade A fistula, five grade B, and one with a grade C fistula.

Patients who developed fistulas had a median amylase level on POD3 of 1380 U/L (183–2248). Among those who did not develop fistulas, the median amylase levels were 94 U/L (18–274). Amylase levels were less than 173 U/L in 13.3% ($n = 2$) of patients who developed fistulas and were higher than 173 U/L in 86.7% ($n = 13$) of those who developed fistulas on POD3. Amylase POD3 levels were unknown for two patients who developed a fistula. (Table 2)

Patients with a firm/hard pancreas texture were 71% (OR = 0.29, 95 CI: 0.08 – 0.95) less likely to form a fistula compared to those patients with a soft pancreas texture ($p = .04$). Patients with a large duct diameter were also 80% (OR = 0.20, 95 CI: 0.02 – 0.89) less likely to form a fistula compared to those patients with a small duct diameter ($p = .03$). Patients with a day three amylase score greater than 173 are 11.46 (95 CI: 2.45 – 53.51) times more

likely to form a fistula compared to those patients with a day three amylase score less than or equal to 173 ($p < .001$). (Table. 3)

Discussion

Recently the use of drain management after PD or DP has become a controversy. Various studies have evaluated the timing of drain removal for patients who have undergone pancreatic resection, and a uniform consensus has not been developed.(12) Furthermore, prophylactic drain placement after surgery is uncommon across many general surgery procedures which have put into question the use of drains after pancreatic surgery. Our aim in this study was to identify a safe time for drain removal based on select patient demographic characteristics, laboratory, and pathologic features. Our study aimed to determine a time for safe drain removal based on three parameters: drain amylase levels, pancreatic texture, and duct size.

Sutcliffe et al. conducted a prospective study of patients undergoing PD. For each patient, amylase levels were measured on POD1 and POD5. They defined a fistula as having an amylase level > 300 U/L on POD5. They demonstrated that patients who developed a POPF had amylase levels on POD 1 that were significantly higher (>350 U/L) than in those without a POPF. They concluded that patients could be stratified according to the likelihood of developing a pancreatic fistula by amylase level. (13) Van Buren et al. conducted a randomized prospective multicenter trial where patients were randomized to PD with and without the use of intraperitoneal drainage. The study found that the elimination of intraperitoneal drainage was associated with an increase in the number of complications per patient (1 vs. 2, $p=0.02$). Also, PD without intraperitoneal drainage was associated with a higher incidence of gastroparesis, intra-abdominal fluid collection, intra-abdominal abscess and prolonged length of stay. (14) Fong et al. conducted a study comparing two cohorts of patients undergoing PD. They found POD1 drain amylase levels lower than 600 U/L (OR 0.0192, $P < 0.001$) was a strong predictor of the absence of a pancreatic fistula. In addition to pancreatic gland texture (OR = 0.193, $P = 0.002$) but not duct diameter (OR 0.861, $P = 0.835$). (10)

McMillan et al. conducted a study which included 260 patients who underwent PD. The risk of developing fistula was determined intraoperatively using a Fistula Risk Score. In patients who were at low-risk of developing fistulas, drains were omitted. Low risk was defined as a score of 1 to 2 points. In those who received a drain, amylase levels were followed postoperatively. Drains were removed on POD3 in patients with POD1 amylase levels $< 5,000$ U/L. The research team found lower rates of fistulas in the study group compared to the control (11.2% vs. 20.6%). Therefore, concluding that POD1 drain amylase levels could identify moderate/high-risk patients that benefit from early drain removal (15) Kawai et al. conducted a study of 104 patients who underwent DP. Patients were assigned to one of two groups in which drains removed on either POD8 or POD4. Patients who had early drain removal had lower rates of intraabdominal infections, abscess, and fluid collections.(16)

Partelli et al. studied 231 patients undergoing PD and DP. Amylase levels were measured POD1 and POD5 (if amylase levels $> 5,000$ U/L on POD1). Patients with POD1 amylase

levels > 200 had the most significant specificity and sensitivity in helping predict fistula formation on POD5. (17) In our study, we evaluated patients who underwent PD and DP and found that the type of surgery was not associated with developing a fistula although amylase levels, pancreatic texture, and duct size predictive. In contrary to Partelli et al. we found amylase levels on POD3 to be predictive.

Our study revealed that drains could be safely removed on POD3 with a high predictive power of not developing a fistula if amylase levels are less than 173 U/L. Furthermore, pancreatic texture and duct size can aid in deciding when to remove the drain safely. Moreover, patients who have persistently elevated amylase levels, higher than 173 U/L on POD3, a high level of suspicion for fistula formation is warranted. We believe selective, and early drain removal should be considered in those who meet our amylase level criteria. The surgeon's judgment of when to safely remove a drain must take into consideration multiple variables like the patients clinical status, biochemical trends, drain character, characteristics of the pancreatic remnant and size of the pancreatic duct. The findings of our study are corroborated by a recent systematic review by Villafane-Ferriol et al. who looked at 14 studies and concluded that drains should be placed routinely and removed early, before POD5, unless the patient's clinical course or drain fluid amylase concentration suggests fistula development. (12)

We like many authors recognize that drain volume is relative and has no relation to whether the patient was developing a POPF. (3) However, the character of the drain output is a different matter. Regardless of the volume, if the character of the drain is turbid or gray we would be cautious in removing the drain especially in patients who have soft pancreatic remnant and a small duct. An assessment of the patient's condition should be conducted, which includes general condition, tolerating a diet, normal white count, and no fever. If a patient meets these criteria than drain removal would be safe.

In the final analysis, we found that patients who have a POD3 amylase level less than of 173 U/L are not at risk of developing a POPF after PD and DP. Also, patients with drains who have amylase levels higher than 173 U/L on POD3 have increased odds of developing a fistula (OR = 11.46, 95% CI: 2.45–53.51) and should not be removed. Lastly, patients who have a firm pancreas and small ducts have lower odds of developing fistulas than those with soft pancreas and small ducts (OR 0.29, p = 0.04, OR = 0.20, p = 0.03).

Conclusions

This study provides insight into helping surgeons decide when is it safe to remove a drain. Our work offers statistical and clinical significance that pancreatic texture, amylase levels, and ducts size help play a role in determining the right time to remove a drain. Amylase levels less than 173 on POD3 supports early drain removal after surgery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlight

1. Seventeen patients developed fistulas (9.4%), with 70.6% (n = 12) developing in soft pancreatic remnants vs. 29.4% (n = 5) in firm pancreatic remnants.
2. Patients with amylase levels greater than 173 U/L on a postoperative day three were 11.46 times more likely to form a fistula compared to those with an amylase level at or below 173 U/L ($p < .001$).
3. Fistula formation is associated with pancreas texture, duct size, and drain amylase following PD or DP.
4. Patients with firm pancreatic texture and large ducts are less likely to develop fistulas than those with soft pancreatic texture and small ducts.

FIGURE 1.
Receiver operator curve for POD3 Amylase Score Examining Fistula Formulation.

TABLE 1

Predicted vs. Actual Fistula Formulation

		Actual		
		Fistula	No Fistula	Total
Predicted	Fistula	13	52	65
	No Fistula	2	93	95
Total		15	145	160

Cut point = 173 to Maximize Sensitivity (87%) and Specificity (64%). Positive Predictive Value (PPV) = 20%. Negative Predictive Value (NPV) = 98%

Table 2

Clinical and operative characteristics of patients

	No Fistula (N = 163)	Fistula (N = 17)	Total (N = 180)
Sex			
Male	87 (53.4%)	11 (64.7%)	98 (54.4%)
Female	76 (46.6)	6 (35.3%)	82 (45.6%)
Age (<i>Mean, SD</i>)	66.1 (12.7)	65.6 (12.2)	66.1 (12.6)
Approach			
Whipple	120 (73.6%)	12 (70.6%)	132 (73.3%)
Distal Pancreatectomy	43 (26.4%)	5 (29.4%)	48 (26.7%)
Pancreas Texture (<i>N</i> = 175)			
Soft	65 (41.1%)	12 (70.6%)	77 (44.0%)
Firm	89 (56.3%)	5 (29.4%)	94 (53.7%)
Hard	4 (2.5%)	0 (0%)	4 (2.3%)
Duct Diameter			
1–3 mm	97 (59.5%)	15 (88.2%)	112 (62.2%)
> 3 mm	66 (40.5%)	2 (11.8%)	68 (37.8%)
Amylase Day 3 (<i>Mdn, IQR</i>)	94 (18–274)	1380 (183–2248)	107 (20–342)
Amylase Day 3 (<i>N</i> = 160)			
< = 173	93 (64.1%)	2 (13.3%)	95 (59.4%)
> 173	52 (35.9%)	13 (86.7%)	65 (40.6%)

Note: Percentages are in parentheses. IQR = Interquartile range.

TABLE 3

Univariable Exact Logistic Regression Model Results Examining Fistula Formulation

	OR	95% CI	P
Sex			
Male	1.60	0.51–5.52	0.53
Female (<i>Ref</i>)			
Approach			
Whipple (<i>Ref</i>)			
Distal	1.16	0.30–3.81	0.99
Pancreatectomy			
Pancreas Texture			
Soft (<i>Ref</i>)			
Firm/Hard	0.29	0.08–0.95	0.04
Duct Diameter			
1–3 mm (<i>Ref</i>)			
> 3 mm	0.20	0.02–0.89	0.03
Age	1.00	0.94–1.06	0.89
Amylase Day 3			
< = 173 (<i>Ref</i>)			
> 173	11.46	2.45–53.51	<.001

Note: 9.4% (or 17 patients) of the 180 patients in the sample formed a fistula.