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ORIGINAL ARTICLE

Prophylactic octreotide for pancreatoduodenectomy: more harm than good?

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Abstract

Background: Most accrued evidence regarding prophylactic octreotide for a pancreatoduodenectomy (PD) predates the advent of the International Study Group of Pancreatic Fistula (ISGPF) classification system for a post-operative pancreatic fistula (POPF), and its efficacy in the setting of high POPF risk is unknown. The Fistula Risk Score (FRS) predicts the risk and impact of a clinically relevant (CR)-POPF and can be useful in assessing the impact of octreotide in scenarios of risk.

Methods: From 2001–2013, 1018 PDs were performed at four institutions, with octreotide administered at the surgeon's discretion. The FRS was used to analyse the occurrence and burden of POPF across various risk scenarios.

Results: Overall, 391 patients (38.4%) received octreotide. A CR-POPF occurred more often when octreotide was used (21.0% versus 7.0%; $P < 0.001$), especially when there was advanced FRS risk. Octreotide administration also correlated with an increased hospital stay (mean: 13 versus 11 days; $P < 0.001$). Regression analysis, controlling for FRS risk, demonstrated that octreotide increases the risk for CR-POPF development.

Conclusion: This multi-institutional study, using ISGPF criteria, evaluates POPF development across the entire risk spectrum. Octreotide appears to confer no benefit in preventing a CR-POPF, and may even potentiate CR-POPF development in the presence of risk factors. This analysis suggests octreotide should not be utilized as a POPF mitigation strategy.

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Introduction

A post-operative pancreatic fistula (POPF) and the clinical consequences of its sequelae after a pancreatoduodenectomy (PD) have been well documented in the literature.[1–4] Numerous mitigation strategies for a POPF are available to the surgeon, including the use of somatostatin analogues, such as octreotide,[5–8] with the putative effect of inhibiting both gastric and pancreatic exocrine secretion.[9–12]

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Early biochemical investigation focused on somatostatin's ability to ameliorate pancreatitis through the inhibition of exocrine function;[13,14] in spite of inconclusive findings, other studies suggested a benefit for reducing the incidence of post-operative complications.[15] Octreotide is a potent inhibitor of pancreatic exocrine secretion, and as pancreatic enzyme secretion is proposed as a driver of fistulae, some advocate its use as a prophylactic measure.[5,16]

In fact, the use of octreotide during a pancreatic resection has been studied extensively, even to the level of eight high-accrual (> 100 cases), randomized-controlled trials.[5–8,17–20] In spite of extensive scrutiny, octreotide's efficacy remains controversial. Büchler's landmark study showed that octreotide was beneficial

for reducing the rate of fistulae; however, it had the following limitations: (i) it failed to delineate between biochemical fistulae and those we now consider clinically relevant; (ii) it analysed both PD and other forms of pancreatic resection together; and (iii) the risk-adjustment process was limited only to disease pathology.[5] The analysis did not account for other currently validated risk factors for the development of a clinically relevant (CR)-POPF such as soft gland parenchyma, small pancreatic duct size and elevated intra-operative blood loss, which contribute to the Fistula Risk Score (FRS).[21,22]

In contrast, studies by both Yeo *et al.* and Sarr *et al.* failed to demonstrate clinical and economic value to somatostatin analogues for post-operative pancreatic fistula mitigation.[18,19] Importantly, all eight of these major studies are now over a decade old and therefore predated the establishment of the International Study Group of Pancreatic Fistula (ISPGF) fistula classification framework, which established a clear dichotomy between a biochemical and clinically-relevant fistula.[2] One study, published since the advent of the ISGPF schema, argued for the selective use of prophylactic octreotide, citing a lack of both clinical effect and cost-containment in low-risk scenarios;[23] however, the study occurred before the development of the FRS and it was a single-institution experience.

This large, multi-centre experience aimed to examine the efficacy of prophylactic octreotide for PD using ISGPF definitions for a clinically relevant fistula. In addition, the FRS, a highly validated tool for predicting the occurrence of a CR-POPF, was used for risk adjustment.[24]

Methods

In accordance with guidelines for human subjects' research, this study was approved by the Institutional Review Board (IRB) at the Hospital of University of Pennsylvania. Records for consecutive patients who underwent a proximal pancreatectomy for all indications were reviewed from prospectively collected databases at four high-volume, academic pancreatic surgical practices (six surgeons), between 2001 and 2013. Two hundred and twenty-seven of the patients have previously been described in a single-centre review of octreotide use.[23]

Surgical approach

All procedures were performed with duct-to-mucosa pancreaticojejunostomy reconstruction; alternative methods of reconstruction (PG) were excluded from this study. Anastomotic stents and drains were used at the surgeon's discretion. Drain amylase levels were recorded on post-operative day (POD) 3 and, in the case of multiple drains, the highest concentration of drain amylase was used to ascertain whether at least a biochemical (Grade A) POPF had occurred. Drains were removed most often after tolerance of a regular diet (POD 5–7), but at the surgeon's discretion. Early drain removal, based on drain amylase levels at POD 3 or earlier, was not practiced in this series.

When prophylactic octreotide [Sandostatin LAR (Novartis Pharma, Novartis AG, Basel, Switzerland) 150 μg subcutaneously] was used, it was initiated intra-operatively by the surgeon at the point of construction of the pancreaticojejunal anastomosis and continued post-operatively every 8 h for 7 days.

Data collection and fistula classification

Outcomes were measured up to 90 days post-operation, including pancreatic fistula occurrence, mortality, duration of stay and readmission. Complications were assessed using the Modified Accordion Severity Grading System.[25] Previously validated risk factors for the development of a CR-POPF[21,22] were recorded for each patient. These pre- and intra-operative variables include pancreatic parenchyma texture, disease pathology (high risk = anything other than pancreatic adenocarcinoma or pancreatitis), duct diameter (measured intra-operatively) and intra-operative blood loss. Each risk factor is associated with a weighted score in accordance with odds ratios (ORs) established by Callery *et al.* (Table 1).[22] The relative value of each risk factor was summated to calculate a FRS (0–10) for each individual patient. FRSs were then discretized and allocated to one of four risk zones: negligible risk (0 points), low risk (1–2 points), moderate risk (3–6 points) and high risk (7–10 points). Each zone reflects distinct tiers of CR-POPF risk based on the aggregate of weighted endogenous and operative risk factors.

Fistula severity was assigned in accordance with the tenants of the International Study Group of Pancreatic Fistula (ISGPF) classification framework;[2] individual grades were computed using the Pancreas Club calculator.[26] The ISGPF defined the threshold for the occurrence of POPF as drainage from an operatively placed drain

Table 1 Fistula Risk Score for the prediction of clinically-relevant fistula (CR-POPF) after pancreatoduodenectomy

Risk factor	Parameter	Points
Gland texture	Firm	0
	Soft	2
Pathology	Pancreatic adenocarcinoma or pancreatitis	0
	Ampullary, duodenal, cystic, islet cell, etc.	1
Pancreatic duct diameter	≥ 5 mm	0
	4 mm	1
	3 mm	2
	2 mm	3
	≤ 1 mm	4
Intra-operative blood loss	≤ 400 ml	0
	401–700 ml	1
	701–1000 ml	2
	>1000 ml	3
		Total 0 to 10 points

From Callery *et al*. *JACS*, 2013.

(or subsequently placed percutaneous drain), on or after POD 3, with an amylase concentration greater than three times the upper limit of normal serum amylase (> 300 IU/l). When POPFs occurred in this series, they were segregated into two categories (biochemical or clinically-relevant) and three grades (A, B or C). Biochemical fistulae (Grade A) are transient and asymptomatic, characterized only by elevated drain amylase levels and they have no significant clinical sequelae.[2,27] In contrast, CR-POPFs (Grades B and C) are more morbid and demonstrate deviation from normal clinical management. Grade B fistulae are symptomatic fistulae, which require diagnostic evaluation and therapeutic management. The spectrum of treatment measures include: antibiotic therapy, therapeutic (non-prophylactic) octreotide, supplemental nutrition (TPN), maintenance of operatively placed drains > 21 days, additional percutaneous drainage, or endoscopic/interventional radiology procedures.[2] Grade C fistulae manifest a significant deviation from the normal clinical pathway, in the form of an operative intervention under general anaesthesia. These particularly severe fistulae can also lead to sepsis, organ failure or death.[2]

Study endpoint

The primary endpoint of this study was to test the null hypothesis that the administration of octreotide does not significantly reduce the occurrence of CR-POPF after a PD. Secondary endpoints included investigating the effects of octreotide on hospital duration of stay, major morbidity (Accordion Grades ≥ 3) and mortality.

Statistical analysis

Comparative analyses between cohorts were conducted using χ^2 or Fisher's exact tests for categorical variables and Student's *t*-test or Wilcoxon's signed-rank test for continuous variables. *P*-values less than 0.05 were considered statistically significant. A multivariable regression was performed adjusting for endogenous and intra-operative CR-POPF risk factors. All candidate predictive variables were entered via forward stepwise regression ($P < 0.05$ for entry) and those variables demonstrating no independent association ($P > 0.10$) with the outcome of a CR-POPF were removed. All statistical computations were performed utilizing IBM SPSS, version 21 (SPSS Inc., Chicago, IL, USA).

Results

Patients, octreotide use and general outcomes

One thousand and eighteen consecutive PDs were performed by six surgeons (range: 5–307) at four institutions (range: 130–445). Trans-anastomotic stents were used in 557 (54.7%) patients, with the internal variety selected 80.6% ($n = 449$) of the time. One or more Blake drains were placed adjacent to the pancreaticojejunal anastomosis in 886 (87.0%) patients. Three hundred and ninety-one patients (38.4%) received prophylactic octreotide. One surgeon ($n = 136$) always applied octreotide, two surgeons ($n = 307$, 86) never used it and three employed it selectively (octreotide: $n = 155$, 97, 3; no octreotide: $n = 139$, 93, 2).

The utilization of octreotide was distributed unevenly across the FRS risk zones: negligible – 9.2%; low – 23.8%; moderate – 61.9%; and high – 5.1%. By comparison, the breakdown of the no-octreotide cohort was: negligible – 18.5%; low – 32.4%; moderate – 42.7%; high – 6.4%. Table 2 shows the frequency of octreotide's administration within each FRS risk zone.

In the overall series, any Accordion complication occurred in 63.5% of the patients; the incidence of Accordion severity grades ≥ 3 was 22.0%. The median duration of stay for the entire study population was 8 days [interquartile range (IQR) 5.0]. Reoperation was necessary in 6.5% of the patients and the 90-day readmission rate was 17.8%. There were 24 (2.4%) mortalities within 90 days.

Risk factors for a CR-POPF

High-risk pathology was encountered more frequently in the octreotide cohort ($P < 0.001$). Additionally, soft gland texture was evident more often in the octreotide cohort (58.5% vs. 41.5%; $P < 0.001$); however, there were no significant differences in terms of pancreatic duct diameter and intra-operative blood loss (Table 2).

Fistula occurrence

Overall, 245 patients developed a POPF (24.1%), of which, 126 were clinically relevant (12.4%; Grade B – 10.1%; and Grade C – 2.3%). The number of FRS risk factors present in any given patient correlated strongly with CR-POPF occurrence: none – 0%; one – 5.6%; two – 10.4%; three – 22.9%; and four – 30.3%. The risk factor most strongly associated with CR-POPF occurrence was soft gland texture (20.4%; $P < 0.001$), closely followed by high-risk pathology (19.5%; $P < 0.001$), duct diameter ≤ 4 mm (16.4%; $P < 0.001$) and intra-operative blood loss > 400 ml (16.3%; $P = 0.023$). The mean, median and mode of the FRS were 3.10, 3.00 and 1.00, respectively.

Comparison of the two treatment cohorts revealed octreotide was associated with higher rates of an overall POPF (28.1% vs. 21.5%; $P = 0.017$) (Table 3). Additionally, a CR-POPF occurred more frequently in patients receiving octreotide (21.0% versus 7.0%; $P < 0.001$). In contrast, the rate of a biochemical fistula was significantly less when octreotide was administered (7.2% versus 14.5%; $P < 0.001$).

Patients in the octreotide cohort experienced higher rates of CR-POPF in the presence of each FRS risk factor (Table 4); this pattern continued when analysing CR-POPF occurrence using the calculated FRS (Fig. 1). Patients receiving octreotide experienced higher rates of CR-POPF across each FRS Risk Zone (Fig. 2). Notably, when octreotide was not employed, fistula occurrence increased linearly with escalating risk; whereas, there was an exponential increase in CR-POPF rates across the zones when octreotide was used.

Forward stepwise regression revealed predictors of CR-POPF: the use of octreotide (OR: 2.6; $P < 0.001$), a lack of routine drain placement (OR: 2.3; $P = 0.003$) and increasing FRS (OR: 1.5 per

Table 2 Endogenous and intra-operative clinically relevant-post-operative pancreatic fistula (CR-POPF) risk factors and distribution of fistula risk

n (%) or mean (SD)	Overall	No octreotide	Octreotide	*P*-value[a]
Pathology				
Pancreatic adenocarcinoma	407 (40.0)	277 (44.2)	130 (33.2)	<0.001
Cystic neoplasm	151 (14.8)	91 (14.5)	60 (15.3)	0.717
Pancreatitis	130 (12.8)	94 (15.0)	36 (9.2)	0.007
Ampullary carcinoma	110 (10.8)	61 (9.7)	49 (12.5)	0.161
Benign lesion	51 (5.0)	12 (1.9)	39 (10.0)	<0.001
Cholangiocarcinoma	48 (4.7)	26 (4.1)	22 (5.6)	0.279
Duodenal Carcinoma	39 (3.8)	18 (2.9)	21 (5.4)	0.043
Other lesions	39 (3.8)	28 (4.5)	11 (2.8)	0.182
Islet cell tumour	35 (3.4)	17 (2.7)	18 (4.6)	0.107
Metastatic lesion	8 (0.8)	3 (0.5)	5 (1.3)	0.272
Soft gland texture	514 (50.5)	260 (41.5)	367 (58.5)	<0.001
Duct size (mm)	4.2 (1.9)	4.2 (1.8)	4.1 (2.0)	0.553
Intra-operative blood loss (ml)	397 (578)	409 (694)	380 (313)	0.440
Fistula risk zone				
Negligible	152 (14.9)	116 (76.3)[b]	36 (23.7)[b]	<0.001
Low	296 (29.1)	203 (68.6)	93 (31.4)	0.003
Moderate	510 (50.1)	268 (52.5)	242 (47.5)	<0.001
High	60 (5.9)	40 (66.7)	20 (33.3)	0.405

[a]Comparing treatment with octreotide versus no octreotide.
[b]Percentage reflects contribution to the total number of patients in the overall series within each risk zone.

unit increase; $P < 0.001$) (Fig. 3 and Table 5). The use of octreotide correlated with the increased incidence of CR-POPF, but it also corresponded to lower rates of biochemical fistula. In the absence of octreotide, Grade A fistulae occurred more frequently with escalating risk; however, when octreotide was administered, rates of biochemical fistula levelled out (Fig. 4).

Other outcomes

Overall morbidity was not significantly different between the two cohorts; however, complications with an Accordion severity grade ≥ 3 occurred more frequently in the octreotide cohort (28.9% versus 17.7%; $P < 0.001$). Patients in both treatment groups with negligible and low fistula risk had similar rates of Accordion severity grades ≥ 3 (octreotide: 17.8% versus control: 15.4%; $P = 0.519$); yet, differences arise among moderate- and high-risk patients, where octreotide correlated with higher rates of these more morbid complications (34.4% versus 20.1%; $P < 0.001$).

The post-operative course also revealed octreotide to be associated with higher rates of re-operation, peri-operative blood transfusion, percutaneous drain placement, TPN supplementation and Intensive Care Unit transfer (Table 3). Adjusting for fistula risk explained some of these differences, but octreotide still trended with higher rates across the risk spectrum (percutaneous drain placement, peri-operative transfusion: $P < 0.001$; TPN: $P = 0.015$; ICU transfer: 0.031; re-operation: $P = 0.111$).

The median duration of stay was significantly greater for patients receiving prophylactic octreotide [9 (IQR 6.0) versus 8 days (IQR 4.0); $P < 0.001$], yet 90-day mortality and readmission were not different between the two treatment cohorts.

Discussion

This study shows that prophylactic octreotide is strongly associated with a greater incidence of a CR-POPF, Accordion complication severity grades ≥ 3, re-operation and an increased duration of hospital stay. In particular, the study found octreotide to correlate with significantly higher rates of a CR-POPF among patients with moderate and high fistula risk – the very cases with which many would expect the greatest efficacy. The occurrence of a CR-POPF was 15.5% and 47.5% greater among moderate- and high-risk patients, respectively. This disparity revealed an exponential relationship between escalating risk and CR-POPF occurrence among patients in the octreotide treatment cohort. In contrast, CR-POPF incidence increased linearly with risk in the cohort not receiving octreotide.

These associations are similar to those found by Lowy *et al.*, who concluded that routine use of octreotide after PD should not be recommended.[17] In that prospective study, 110 patients were randomized to prophylactic octreotide or no further treatment. In spite of pre-dating the advent of the ISGPF fistula classification

Table 3 Post-operative outcomes

n (%) or median (interquartile range)	Overall		
	No octreotide	Octreotide	*P*-value
Patients	627 (61.6)	391 (38.4)	–
POPF	135 (21.5)	110 (28.1)	0.017
CR-POPF	44 (7.0)	82 (21.0)	<0.001
ISGPF classification			
Grade A	91 (14.5)	28 (7.2)	<0.001
Grade B	36 (5.7)	67 (17.1)	<0.001
Grade C	8 (1.3)	15 (3.8)	0.007
Any complication, *N* (%)	395 (63.0)	251 (64.2)	0.700
Accordion severity grade ≥ 3, *N* (%)	111 (17.7)	113 (28.9)	<0.001
Performance measures			
Hospital transfusion	144 (23.0)	155 (39.6)	<0.001
Percutaneous drain placement	24 (3.8)	55 (14.1)	<0.001
TPN	121 (19.3)	106 (27.1)	0.004
Re-operation	33 (5.3)	33 (8.4)	0.045
ICU transfer	45 (7.2)	46 (11.8)	0.013
Mortality – 90 days	13 (2.1)	11 (2.8)	0.525
Readmission – 90 days	106 (16.9)	75 (19.2)	0.356
Duration of stay (days)	8 (7–11)	9 (8–14)	<0.001

PDOD, post-operative pancreatic fistula; CR-POPF, clinically relevant-post-operative pancreatic fistula; ISGPF, International Study Group of Pancreatic Fistula; TPN, total parenteral nutrition; ICU, intensive care unit.

Table 4 Clinically relevant fistula occurrence in the presence of fistula risk factors

FRS risk factor	No octreotide	Octreotide	*P*-value
	CR-POPF, *n* (%)	CR-POPF, *n* (%)	
Patients	627 (61.6)	391 (38.4)	–
High-risk pathology[a]	27 (10.5)	67 (29.8)	<0.001
Soft gland texture	32 (12.3)	73 (28.7)	<0.001
Duct size risk factor (≤ 4 mm)	35 (9.2)	68 (27.2)	<0.001
Duct size			
≥ 5 mm	9 (3.6)	14 (9.9)	0.011
4 mm	14 (9.7)	14 (19.4)	0.045
3 mm	6 (4.8)	25 (23.4)	<0.001
2 mm	13 (14.6)	25 (39.7)	0.001
≤1 mm	2 (10.0)	4 (50.0)	0.038
Blood loss risk factor (> 400 ml)	15 (9.4)	28 (27.2)	<0.001
Intra-operative blood loss			
≤400 ml	29 (6.2)	54 (18.8)	<0.001
401–700 ml	10 (10.3)	16 (23.2)	0.024
701–1000 ml	3 (7.7)	6 (28.6)	0.054
>1000 ml	2 (8.3)	6 (46.2)	0.013

[a]Any pathology exclusive of pancreatic adenocarcinoma or pancreatitis. CR-POPF, clinically relevant-post-operative pancreatic fistula; FRS, Fistula Risk Score.

system, this study delineated between biochemical and clinically relevant fistulae. Biochemical leaks were defined as elevated drain-amylase (> 2.5 normal upper limit of normal for serum amylase) after POD 3 – very similar to the same ISGPF definition. Clinically significant fistulae met the specifications for a biochemical fistula, but also had to be accompanied by fever, leukocytosis, sepsis or the need for percutaneous drainage. Using these definitions, they found the rate of a clinically significant fistula to be lower in the absence of octreotide (6% versus 12%; $P = 0.23$).[17] The study also found no significant differences between the treatment groups in terms of overall morbidity, duration of hospital stay and mortality.

Several years later, a study by Yeo *et al.* corroborated the findings of Lowy *et al.* That single-centre study randomized 211 patients to either prophylactic octreotide or saline. Pancreatic fistulae were defined as drainage of amylase-rich fluid > 3 times the upper limit of normal serum after POD 10, or pancreatic anastomotic disruption observed from radiographical imaging.[18] The rates of pancreatic fistula were 9% in the control group compared to 11% in the cohort receiving octreotide. Overall morbidity was also greater in the octreotide group (40% versus 34%), along with mortality (1% versus 0%); the median duration of stay was equivalent between treatments. A cost analysis also concluded that the elimination of octreotide would be beneficial.

Contrary to the findings of this present study, four randomized, controlled, multicentre studies from Europe, all almost 20 years old, found octreotide to be beneficial for reducing the occurrence of a fistula;[5–8] in spite of the congruence of their arguments, each study has been criticized for significant limitations.[28] First, the liberal definition for a fistula in each of these studies aligns with what is now considered the threshold for a biochemical fistula. As biochemical leaks are asymptomatic and resolve without sequelae, it is necessary to classify a pancreatic fistula into subcategories that speak to their clinical significance. The results of this present study demonstrated that octreotide was associated with significantly lower rates of a biochemical fistula, whereas also strongly correlating with elevated rates of CR-POPF. In a smaller sample size, these opposing trends could possibly cancel each other out and make octreotide appear to have no effect on *overall* pancreatic fistula occurrence.

A recent Cochrane Collaboration addressed the issue of fistula nomenclature while attempting to ascertain the efficacy of somatostatin analogues; however, the analysis could only find three published randomized-controlled studies in which clinically relevant fistulae were distinguished from biochemical leaks, and only one of them used the ISGPF construct.[29] In two of the three

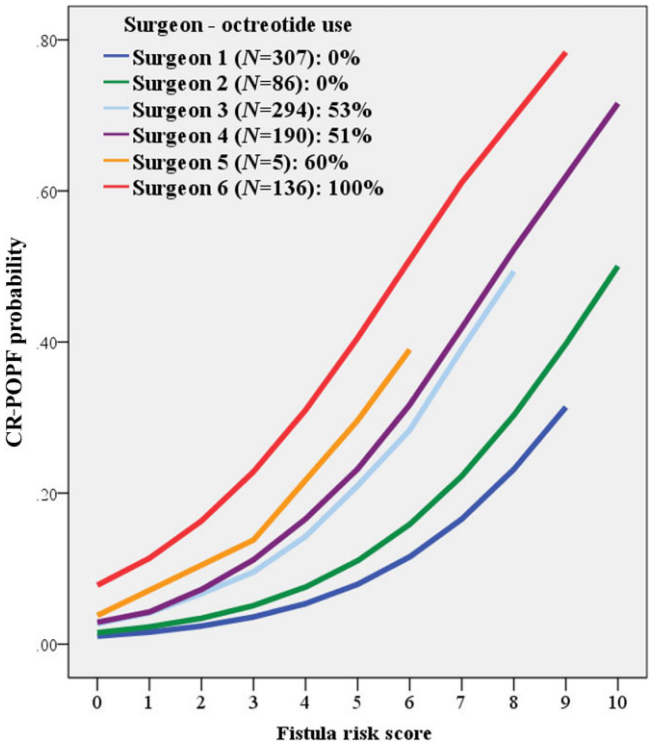

Figure 1 Surgeon octreotide use and their clinically relevant-post-operative pancreatic fistula (CR-POPF) probabilities across the spectrum of fistula risk

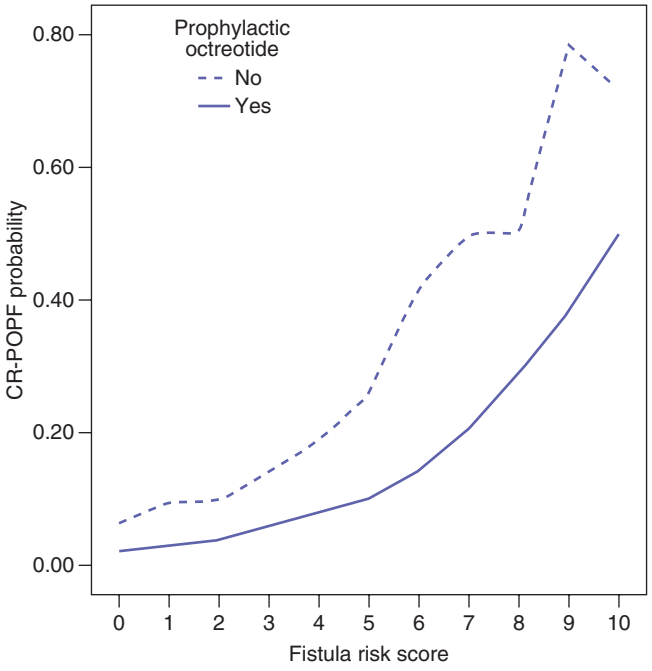

Figure 3 Probability of clinically relevant fistula across the Fistula Risk Score. Octreotide use – odds ratio (OR): 2.6, $P < 0.001$; Fistula Risk Score – OR: 1.494 per unit increase, $P < 0.001$

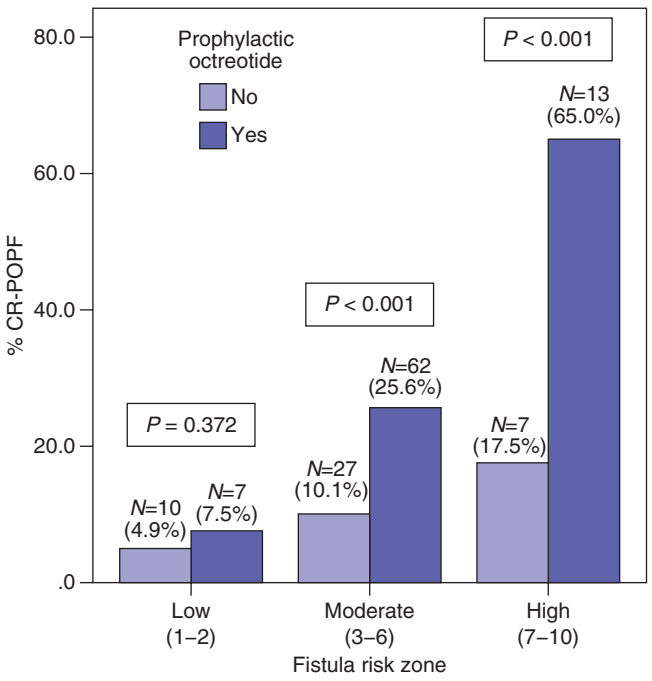

Figure 2 Clinically relevant fistula occurrence across the Fistula Risk Score (FRS) Risk Zones

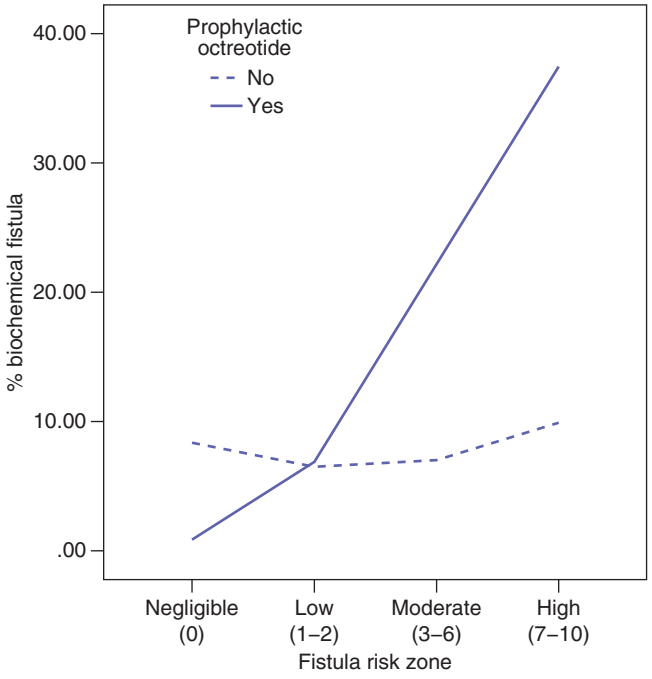

Figure 4 Biochemical fistula occurrence across the Fistula Risk Score (FRS) Risk Zones. Negligible risk: $P = 0.042$; low risk: $P = 0.887$; moderate risk: $P < 0.001$; high risk: $P = 0.026$

Table 5 Multivariate analysis for predictors of a clinically relevant fistula

Variable	*P*-value	OR (95% CI)
Fistula Risk Score	<0.001	1.5 (1.4–1.6)
Prophylactic octreotide	<0.001	2.6 (1.7–4.0)
Intra-operative drain(s)	0.003	0.4 (0.3–0.8)
Trans-anastomotic stent	0.182	–
Surgeon factors		
Years of experience	0.715	–
Pancreatoduodenectomies performed	0.453	–

OR, odds ratio; CI, confidence interval.

studies, the rates of clinically relevant fistulae were higher in the octreotide cohort.[30,31] The third study, conducted by Gouillat *et al.*,[32] found octreotide to lower the incidence of clinically relevant fistulae, yet it has been cited for a high risk of bias.[29] An additional limitation of that particular study was its modest overall sample size ($n = 75$).

Another shortcoming of these studies was that all of the trials included many types of pancreatic resections.[5–8] Risk factors for a clinically relevant fistula vary depending on the type of pancreatic resection and an inclusive analysis could distort the interpretation of fistula outcomes for a PD.[3] The study by Montorsi *et al.* was the only one to conduct subset analyses based on the type of pancreatectomy. Not surprisingly, the frequency of fistula varied between procedures and differences between treatments became non-significant for a PD (control: 14.9%; octreotide: 10.5%), whereas octreotide was associated with fewer fistulae after a distal pancreatectomy (6.0% versus 21.2%) and enucleations (0% versus 57.1%).[7]

The final major limitation of the studies that support octreotide use, and also many of the recent retrospective studies,[16,33] is the absence of a comprehensive risk adjustment process. Most of the early literature was largely limited to univariate analyses, and even recent retrospective works have excluded highly validated risk factors, such as soft gland and duct size, when conducting multivariable testing.[16] Our study addressed this issue by utilizing the externally validated FRS, which has shown a strong capacity to predict CR-POPFs;[24] this metric adjusted for endogenous and operative fistula risk when comparing the clinically relevant outcomes between treatment cohorts.

Biological explanations for the results of our study can be found throughout the bench science and translational literature. The foremost factor mentioned is the effect of octreotide on splanchnic blood flow; multiple studies have correlated octreotide with decreased pancreatic perfusion and gastroduodenal mucosal blood flow.[10,11,34–39] This regionalized ischaemia could limit or impair wound healing at the site of the anastomosis.[40] Many of these previous studies were conducted with intravenous, rather than subcutaneous, administration of somatostatin and its analogues; however, a study by Eriksson *et al.* demonstrated that both intravenous and subcutaneous administration of a long-acting somatostatin analogue decreased splanchnic blood flow by 20–25% in human subjects.[41]

Second, octreotide has been shown to suppress the secretion of anabolic and tropic hormones such as pituitary growth hormone (GH), insulin-like growth factor 1 (IGF-1) and epidermal growth factor (EGF), all of which facilitate the wound-healing process.[9,42–44] An earlier work by Konturek *et al.* demonstrated that EGF inhibition causes a delay in the healing of gastrointestinal ulcers; the study attributed these findings to the important mitogenic effects of EGF.[45] A study by Waddell *et al.* even compared the impact octreotide has on wound healing to that of immunosuppressive steroids.[46]

Additionally, Jenkins *et al.* observed subcutaneous administration of octreotide to decrease the volume of pancreatic juice, while also causing large fluctuations in enzyme concentration. That study concluded that a low volume of pancreatic juice with high enzyme concentrations might delay fistula closure.[47] The answer for octreotide's association with higher rates of CR-POPF is almost certainly multifactorial and cannot be conclusively defined by a single physiological mechanism.

There are several limitations to this present study, such as the absence of a randomization process with the administration of octreotide; it was administered at the surgeon's discretion. This first limitation was addressed through the use of the FRS to compare patients with similar risk profiles for CR-POPF development. An additional limitation was that octreotide usage was not normally distributed between surgeons. To minimize this potential source of bias, the multivariate model considered other potential confounding factors such as surgeon years of experience, the use of trans-anastomotic stents and routine intraperitoneal drain placement.

Conclusion

In this assessment of octreotide for a PD, the largest to date, it appears that when looking through the prism of risk adjustment, not only is octreotide ineffective at mitigating a CR-POPF, it might actually potentiate risk. To conclude, these data suggest that octreotide should not be used as a fistula mitigation strategy.

Conflicts of interest

None declared.

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