Outcomes after Pancreatectomy with Routine Pasireotide Use

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BACKGROUND: Morbidity after pancreatectomy is commonly due to leakage of exocrine secretions resulting in abscess or pancreatic fistula (PF). Previously, we authored a double-blind randomized controlled trial demonstrating that perioperative pasireotide administration lowers abscess or PF formation by >50%. Accordingly, we adopted pasireotide use as standard practice after pancreatectomy in October 2014 and hypothesized a similar PF/abscess rate reduction would be observed.

STUDY DESIGN: A prospectively maintained database was queried for all patients who underwent pancreatectomy between October 2014 and July 2017. Pasireotide was administered preoperatively and twice daily for 7 days postoperatively or until discharge. The primary end point was clinically relevant PF/abscess requiring procedural intervention, identical to the earlier trial outcomes. Logistic regression was used to compare outcomes with the placebo arm of the earlier randomized trial and to control known PF risk factors.

RESULTS: During the 34-month study period, 652 patients underwent pancreatectomy (211 distal pancreatectomy, 441 pancreaticoduodenectomy). Compared with the historical placebo group (n = 148), the observational group had an increased prevalence of higher American Society of Anesthesiologists scores (69% vs 54%; $p < 0.001$) and high-risk cases (small duct and soft gland, 47% vs 36%; $p = 0.030$). The primary end point occurred in 13.3% of patients receiving pasireotide vs 20.9% in the placebo arm of the earlier trial trial (odds ratio 0.58; 95% CI 0.37 to 0.92; $p = 0.020$). Biliary leakage was lower in those receiving pasireotide (0.6% vs 3.4%; $p = 0.014$), and other morbidity was unchanged. No subpopulation was identified more likely to benefit from pasireotide.

CONCLUSIONS: At our center, adoption of pasireotide has allowed us to achieve a clinically significant abscess or pancreatic leak rate of 13.3%, approximating the effect observed in the randomized trial of pasireotide during routine surgical practice.

In the modern era, pancreatectomy is performed safely at major centers, with a mortality <2%. However, major morbidity continues to occur in >30% of patients, many of whom experience pancreatic leakage and resultant sequelae.[1,2] Although many operative techniques or other adjuncts purporting to decrease fistula- or other leak-related morbidity have been described, no one technique has proven widely effective, and interest in novel strategies to mitigate leakage after pancreatectomy remains high.[3,4] The prototype somatostatin analogue, octreotide, was first reported in 1982 and remains in widespread clinical use.[5,6] Octreotide has been demonstrated to decrease the volume and potency of both pancreatic exocrine secretions and hormone production.[7] As the major cause of morbidity after pancreatectomy is leakage of pancreatic exocrine secretions, this finding provided a rationale for perioperative

CME questions for this article available at http://jacscme.facs.org

Disclosure Information: Authors have nothing to disclose. Timothy J Eberlein, Editor-in-Chief, has nothing to disclose.

Presented at the Americas Hepatopancreatobiliary Association Annual Meeting, Miami Beach, FL, March 2018.

Received August 16, 2018; Revised October 18, 2018; Accepted October 19, 2018.

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https://doi.org/10.1016/j.jamcollsurg.2018.10.018
ISSN 1072-7515/18

Abbreviations and Acronyms

ASA = American Society of Anesthesiologists
ISGPS = International Study Group for Pancreatic Surgery
MSKCC = Memorial Sloan Kettering Cancer Center
OR = odds ratio

administration of octreotide to decrease leakage-related complications, such as pancreatic fistula or abscess formation.[8,9] Although some European trials identified a benefit associated with octreotide administration after pancreatic resection, Western studies and meta-analyses have largely demonstrated that the incidence of clinically relevant pancreatic leakage is not significantly altered.[10-14]

Octreotide has demonstrated activity at only 1 of the 5 (sst2) endogenous somatostatin receptors present in humans. This could possibly explain the lack of reduction in postoperative pancreatic fistula or abscess formation after administration of octreotide after pancreatic resection. The novel analogue, pasireotide, has activity at 4 somatostatin receptors (sst1 to sst3, sst5), a longer half-life, and demonstrated reduction in exocrine pancreatic secretion in animal models.[15,16] We evaluated the effectiveness of pasireotide to reduce the incidence of pancreatic leak, fistula, and abscess formation after pancreatic resection in a double-blind randomized controlled trial reported in 2014.[17] The primary end point was limited to clinically relevant morbidity requiring procedural intervention and demonstrated a statistically significant absolute risk reduction of 12%, from 21% in the placebo group to 9% in those receiving pasireotide.

Since this trial was reported, our center adopted routine perioperative pasireotide use after all pancreatic resections. Other single-institution non-randomized experiences describing the results of perioperative pasireotide administration have not duplicated the results of the randomized trial.[18,19] As such, the primary aim of this study was to assess the incidence of clinically relevant pancreatic leak, fistula, and abscess formation in patients undergoing pancreatic resection since the initiation of routine perioperative pasireotide administration at our institution. To best inform this effort, the placebo-receiving arm of the previous randomized trial served as a comparison cohort. Secondary aims included evaluating trends and adherence with the treatment regimen and checking for interactions to assess if any subgroups derived differential benefit from pasireotide.

METHODS

Patient selection

The study period began when routine perioperative pasireotide use was initiated in October 2014 and continued until June 2017. Adult patients undergoing either pancreaticoduodenectomy or distal pancreatectomy with or without splenectomy were included. Exclusion criteria were limited to patients that did not receive a single dose of pasireotide during their hospital stay and those who did not ultimately undergo resection. All patients underwent appropriate cardiac risk stratification for major abdominal operation, but patients were not excluded based on ECG criteria, as the previous trial demonstrated no adverse cardiac events. This study was approved by the IRB of Memorial Sloan Kettering Cancer Center (MSKCC).[17]

Study design and outcomes assessment

A prospectively maintained database of all consecutive patients undergoing pancreatic resection at MSKCC was queried. The primary end point was aggregate incidence of grade 3 or higher postoperative pancreatic fistula, leak, or abscess at 60 days, as defined by the MSKCC Surgical Secondary Events system. This system has been validated and approximates the National Cancer Institute's Common Terminology Criteria for Adverse Events and other published metrics for surgical morbidity (Table 1).[20,21] Pancreatic leak or fistula required the presence of amylase-rich drain effluent, and diagnosis of abscess required positive microbial cultures. Grade 3 or higher events were defined as those that required postoperative procedural intervention, either percutaneous drain placement/adjustment or re-exploration in the operating room. Patients with operative drains who met the definition of fistula, leak, or abscess were considered as having met the primary end point. These definitions mirror those of the International Study Group for Pancreatic Surgery (ISGPS) for clinically relevant (grade B/C) pancreatic fistula.[22] Secondary outcomes of interest were similarly defined using the MSKCC Surgical Secondary Events reporting system or defined clinically (such as readmission).

For comparison, we used the placebo-receiving group in the randomized controlled trial as a control group because the criteria for inclusion were identical and the surgical technique, ancillary caregivers, and perioperative management were essentially unchanged.[17] In addition, the primary end point—incidence of clinically relevant (grade 3 or higher) pancreatic leak, fistula, or abscess development—was carefully scrutinized and recorded prospectively. Briefly, these patients underwent resection between October 2009 and July 2013 and were assigned to receive placebo via randomly sized permuted blocks to stratify group assignments according to type of procedure (distal pancreatectomy or pancreaticoduodenectomy) and absence or presence of a dilated pancreatic duct (defined

Table 1. Memorial Sloan Kettering Cancer Center Surgical Secondary Events Reporting System's Definition and Grading for Postoperative Pancreatic Fistula, Leak, and Abscess Formation

Complication	Definition	Grade
Pancreatic fistula	Clinical signs and symptoms of pancreatic fistula, with amylase-rich drainage of >50 mL/d after POD 10	1. Oral medication or bedside medical care required 2. IV medical therapy with resolution or antibiotics or total parenteral nutrition required 3. Radiologic, endoscopic, or operative intervention required 4. Chronic deficit or disability associated with the event 5. Death associated with sequelae of this event
Pancreatic anastomotic leak	Clinical signs and symptoms or radiologic confirmation of pancreatic anastomotic leak, with amylase-rich drainage of >50 mL per day after POD 5, without development of a fistula	
Intra-abdominal abscess	Clinical signs and symptoms or radiologic diagnosis of intra-abdominal abscess or peritonitis	

POD, postoperative day.

as >4 mm). All members of the clinical team were blinded to the group assignments during the initial study.

Operative technique and perioperative care

Surgical care was provided by any 1 of 7 experienced pancreatic surgeons; technique was individual to each surgeon. In general, gastro-/duodenojejunostomy was performed in an end to side manner in the antecolic position. Pancreaticojejunostomy was performed in a 2-layer end to side fashion using duct to mucosa reconstruction (Blumgart technique). Preservation of the pylorus or classic (Kausch-Whipple) pancreaticoduodenectomy was at the discretion of the surgeon. Operative drains were used selectively. During distal pancreatectomy, transection was either performed using a stapling device or sharp transection and oversewing of the pancreatic remnant. All patients were cared for on a hospital ward specific to hepatopancreatobiliary surgical care with dedicated nursing and ancillary staff. Nasogastric tubes were used selectively and removed on postoperative day 1 if used; dietary progression to clear liquids was initiated on postoperative day 2 and advanced as tolerated. If used, operative drains were removed at the discretion of the treating surgeon, but generally occurred when the output had amylase concentration of <300 U/L or the volume was <100 mL/d.

All patients in the study group received at least 1 dose of 900 μg subcutaneous pasireotide. The first dose was administered either in the presurgical ward on the day of operation or in the operating room at the time of induction. Pasireotide was continued twice daily for 7 days postoperatively or until discharge, whichever occurred first; these patients were considered to have received a "full dose." For patients with an adverse reaction to pasireotide, dosage was reduced or therapy discontinued; these patients were considered to have received a "partial dose" and the total number of doses received was recorded. Cross-sectional imaging was performed when concern existed for intra-abdominal morbidity and appropriate interventions were sought as needed.

Statistical analysis

Fisher's exact test and Wilcoxon rank-sum test were used to compare characteristics between cohorts. Rates of complications were reported with exact 95% CIs and compared with Fisher's exact test. Univariable and multivariable logistic regression was used to assess the relationship between cohort and primary outcomes complications grade ≥3 (ie pancreatic fistula, leak, or abscess). Known or suspected confounding factors, including age, BMI, sex, American Society of Anesthesiologists (ASA) score, resection type, and pancreatic duct size were controlled for in the multivariable model. Because of the collinearity between pancreatic duct size and gland texture, only gland texture was included in the multivariable model. The relationship among pasireotide administration, known risk factors, and primary complication rate was assessed via logistic regression.

The proportion with exact 95% CI of overall primary complications and grade ≥3 primary complications were stratified by risk factors (eg bile duct size, texture, risk score, and resection type) and visualized with bar charts. The interaction between each risk factor with the overall primary end point was assessed with logistic modeling, including the 2 main effects and interaction term. Two-sided p values <0.05 were considered statistically significant. All analyses were performed with SAS, version 9.4 (SAS Institute).

RESULTS

Patient characteristics

During the nearly 3-year study period, 662 patients underwent pancreaticoduodenectomy or distal pancreatectomy. Of these, 652 (98.6%) patients received at least 1 dose of pasireotide and formed the current study sample. Resection was performed for pancreatic ductal adenocarcinoma in

66.3% of cases. The group that received placebo in the earlier randomized trial of pasireotide consisted of 148 patients and was used for comparison (eTable 1). The current experimental and historical control groups were balanced in age and no significant differences were seen for sex or BMI, as shown in Table 2, although operative blood loss was higher in the placebo group (median 300 mL vs 250 mL; $p < 0.001$). The ASA score was significantly higher in the treatment group with 69.2% (451 of 652) having ASA score of 3 or 4, compared with 54.1% (79 of 146) in the placebo group ($p < 0.001$) (Table 2).

The proportion of patients that underwent distal pancreatectomy (32.4% in each group) vs pancreaticoduodenectomy (67.6% in each group) and had operative drains placed (23.1% vs 25%) were nearly identical. Gland texture and pancreatic duct size were also evaluated. A similar fraction was noted to have small (≤4 mm) ducts in each group, and although the study group had a higher proportion of soft gland texture (60.2% [392 of 651] vs 52.4% [75 of 143]), this difference was not statistically significant ($p = 0.09$). A composite "risk profile" is also shown in Table 2, aggregating these 2 inherent gland characteristics known to be associated with pancreatic leak into low-, moderate-, and high-risk groups, based on the coincidence of soft glands with small ducts. In the aggregate risk score, treatment patients had a higher proportion of high-risk glands (soft gland and small duct, 47.4% [308 of 650]) compared with the placebo patients (36.4% [52 of 143]; $p = 0.030$).

Study outcomes

The primary end point of aggregate grade 3 or higher pancreatic leak, fistula, and abscess formation occurred in 13.3% (95% CI 10.8% to 16.2%) of those receiving pasireotide compared with 20.9% (95% CI 14.7% to 28.4%) of those in the placebo-receiving control group

Table 2. Demographic and Surgical Characteristics of the Study Population Compared with the Historical Placebo-Receiving Control Population

Characteristic	Received pasireotide (n = 652)	Received placebo (n = 148)	p Value
Age, y, median (range)	66 (17–90)	66 (31–89)	0.56
Sex, n (%)			0.24
Female	320 (49.1)	81 (54.7)	
Male	332 (50.9)	67 (45.3)	
Estimated blood loss, mL, median (range)	250 (0–4,500)	300 (25–2,400)	<0.001*
BMI, kg/m^2, median (range)	26.2 (15.5–52.2)	27.8 (18.7–47.3)	0.12
American Society of Anesthesiologists score, n (%)			<0.001*
1–2	201 (30.8)	67 (45.9)	
3–4	451 (69.2)	79 (54.1)	
Operative drain, n (%)			0.67
Yes	150 (23.1)	37 (25)	
No	500 (76.9)	111 (75)	
Resection, n (%)			>0.95
Distal pancreatectomy	211 (32.4)	48 (32.4)	
Pancreaticoduodenectomy	441 (67.6)	100 (67.6)	
Duct size, n (%)			0.14
≤4 mm	368 (56.4)	77 (52)	
4–8 mm	254 (39.1)	59 (39.9)	
≥8 mm	28 (4.3)	12 (8.1)	
Gland texture, n (%)			0.09
Soft	392 (60.2)	75 (52.4)	
Firm	259 (39.8)	68 (47.6)	
Risk profile, n (%)†			0.030*
Low (>4 mm duct, firm)	198 (30.5)	47 (32.9)	
Moderate (≤4 mm or soft)	144 (22.2)	44 (30.8)	
High (≤4 mm and soft)	308 (47.4)	52 (36.4)	

Percentages are derived from cohort totals with available data, excluding unknown data points, which are not displayed.
*Significant.
†Risk profile is a composite estimate of baseline risk for pancreatic leakage based on gland texture and pancreatic duct size (soft gland and smaller duct considered higher risk).

(odds ratio [OR] 0.58; 95% CI 0.37 to 0.92; p = 0.020). The absolute risk reduction of 7.6% reflected a number needed to treat with pasireotide of 13.2 patients to prevent 1 occurrence of the primary end point. As shown in Table 3, in univariable analyses, patients with pancreatic duct size >4 mm were at lower risk of the primary end point (OR 0.60; 95% CI 0.40 to 0.91; p = 0.015) and patients with a higher BMI had higher odds of the primary end point (OR 1.05; 95% CI 1.01 to 1.09, p = 0.007). Soft gland texture was marginally associated with primary end point (OR 1.48; 95% CI 0.98 to 2.24; p = 0.06).

Table 4 displays morbidity related to secondary events of interest. The incidence of biliary leak/fistula was substantially decreased in those receiving pasireotide (0.6%; 95% CI 0.2% to 1.6% vs 3.4%; 95% CI 1.1% to 7.7%; p = 0.014), and the rates of delayed gastric emptying or enteric leaks were similar. Of the individual components of the primary end point, pancreatic leak or fistula incidence decreased from 14.2% to 8.0% (p = 0.02), and abscess incidence decreased from 10.1% to 6.3% (p = 0.11). Grade 1 or 2 pancreatic leak/fistula events (which would be analogous to ISGPS grade A or biochemical leaks) occurred in 4.8% of patients. Postoperative hemorrhage, for which grade 2 complications were considered meaningful (grade 2 being indicative of need for transfusion) was decreased from 8.8% to 4.6% in those receiving placebo and pasireotide, respectively. This trend did not reach significance (p = 0.07). Overall mortality at 90 days was 1.1% and did not differ between groups (p > 0.95).

As mentioned in the Methods, a multivariate logistic regression model was built, but multicollinearity prevented inclusion of both gland texture and pancreatic duct size as independent variables; the resultant model is also demonstrated in eTable 1 with an OR for patients receiving pasireotide of 0.65 (95% CI 0.38 to 1.13; p = 0.13)

Analysis of pasireotide-only cohort

For patients in the pasireotide-receiving cohort, potential risk factors for postoperative pancreatic leak, fistula, or abscess formation were assessed via logistic regression in a separate analysis. A full dose of pasireotide, defined as twice-daily pasireotide for 7 days postoperatively or until discharge (whichever occurs first), was received by 83.4% (544 of 652) (Table 5). Median time of pasireotide administration in those who received partial doses (n = 108) was 5 days (range 1 to 6 days). As shown in Table 5, the primary end point risk did not differ between those receiving a full or

Table 3. Analysis of Risk Factors for the Primary Outcome Measure (Aggregate Incidence of Pancreatic Fistula/Leak/Abscess) Across All Study Participants (n = 800) via Univariable Logistic Regression

Characteristic	At risk		Odds ratio	95% CI	p Value
	Incidence/n	%			
Treatment cohort					
Pasireotide	87/652	13.3	0.58	0.37–0.92	0.020*
Placebo	31/148	20.9	—	—	—
American Society of Anesthesiologists score					
1–2	36/268	13.4	ref	—	—
3	79/507	15.6	1.19	0.78–1.82	0.71
4	3/23	13.0	0.97	0.27–3.42	
Sex					
Female	69/401	17.2	1.48	1.00–2.21	0.050
Male	49/399	12.3	ref	—	—
Resection					
Distal pancreatectomy	40/259	15.4	1.08	0.72–1.64	0.70
Whipple	78/541	14.4	ref	—	—
Gland texture					
Soft	78/467	16.7	1.48	0.98–2.24	0.06
Firm	39/327	11.9	ref	—	—
Duct size					
>4 mm	40/353	11.3	0.60	0.40–0.91	0.015*
≤4 mm	78/445	17.5	ref	—	—
Age at operation, y	118/800	14.8	0.99	0.98–1.01	0.20
BMI, kg/m^2	107/745	14.4	1.05	1.01–1.09	0.007*

*Significant.
ref, reference statistics.

Table 4. Comparison of Secondary Outcomes Measures from Patients in the Study Population vs Those Who Received Placebo

	Pasireotide group (n = 652)			Placebo group (n = 148)			
Secondary outcome	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**p Value**
Biliary leak/fistula	4	0.6	0.2–1.6	5	3.4	1.1–7.7	0.014*
Delayed gastric emptying	30	4.6	3.1–6.5	6	4.1	1.5–8.6	>0.95
Enteric leak/fistula	3	0.5	0.1–1.3	2	1.4	0.2–4.8	0.23
Other morbidity ≥grade 3	45	6.9	5.1–9.1	18	12.2	7.4–18.5	0.041*
Hemorrhage (≥grade 2)	30	4.6	3.1–6.5	13	8.8	4.8–14.6	0.07
Mortality (90 d, any cause)	8	1.2	0.5–2.4	1	0.7	0.0–3.7	>0.95

Only events of grade 3 or higher (those requiring procedural intervention) were considered meaningful, except where indicated.
*Significant.

partial dose (p = 0.18). Conversely, soft gland texture (OR 1.87; 95% CI 1.14 to 3.09; p = 0.014) demonstrated statistically significant increased risk of the primary end point and pancreatic duct size >4 mm demonstrated decreased risk of primary end point (OR 0.61; 95% CI 0.38 to 0.99; p = 0.044). Patients with moderate- or high-risk glands had higher odds of primary end point compared with low-risk patients, although the magnitude of increased risk was similar (OR 2.32/2.31 for moderate-/high-risk; p = 0.019). The most common treatment-limiting toxicity leading to partial-dose administration was nausea. No life-threatening adverse events were attributed to pasireotide.

Subgroup analysis

Figure 1 demonstrates the incidence of the primary end point stratified by these risk factors, in addition to type of resection (distal pancreatectomy vs pancreaticoduodenectomy) and compared with the equivalent group in the placebo-receiving control group. None of the interactions between pancreatic duct size, gland texture, complication risk, or resection time with treatment cohort were found to be significant (p = 0.12 to 0.69) (eTable 2), which mirrors the similar primary end point rates presented in eFigure 1. Although no individual subgroup demonstrated a statistically significant decrease, an absolute risk reduction was observed across all subgroups, with the greatest reduction seen in patients with firm gland texture (12.8%).

DISCUSSION

The primary aim of this study was to assess the incidence of clinically relevant pancreatic leak, fistula, or abscess

Table 5. Analysis of Risk Factors for the Primary Outcome Measure (Aggregate Incidence of Pancreatic Fistula/Leak/Abscess) among Patients in the Study Arm Alone (Received Pasireotide, N = 652) via Univariable Logistic Regression

	At risk				
Characteristic	**Incidence/n**	**%**	**Odds ratio**	**95% CI**	**p Value**
Received full course (14 doses)					
Yes	77/544	14.2	1.62	0.81–3.23	0.18
No	10/108	9.3			
Incremental days on pasireotide	87/652	13.3	1.07	0.86–1.32	0.55
Gland texture					
Soft	63/392	16.1	1.87	1.14–3.09	0.014*
Firm	24/259	9.3	ref	—	—
Duct size					
>4 mm	29/282	10.3	0.61	0.38–0.99	0.044*
≤4 mm	58/368	15.8	ref		
Risk profile					
High (≤4 mm and soft)	49/308	15.9	2.31	1.26–4.24	—
Moderate (≤4 mm or soft)	23/144	16.0	2.32	1.16–4.62	0.019*
Low (>4 mm duct, firm)	15/198	7.6	ref	—	—

A full dose of pasireotide is considered 14 total doses given twice daily or continued administration until discharge, whichever occurs earlier.
*Significant.
ref, reference statistics.

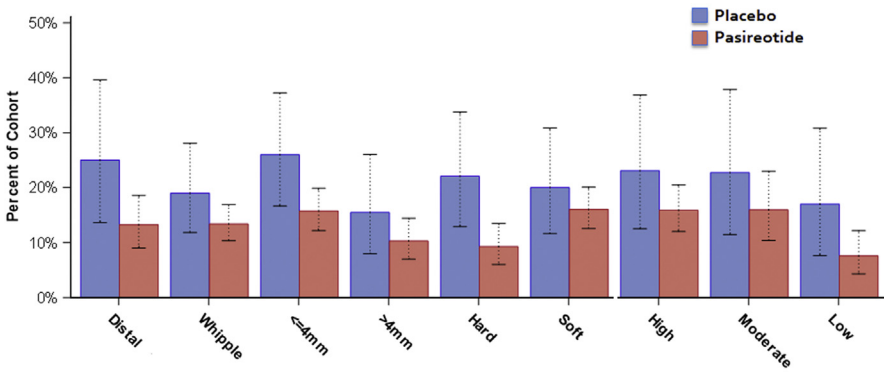

Figure 1. Incidence of the primary end point (aggregate incidence of pancreatic fistula/leak/abscess) in the current study population routinely receiving pasireotide vs the control population that received placebo. Error bars indicate 95% CI.

formation after pancreatic resection with routine perioperative administration of the somatostatin analogue pasireotide. There were 652 patients evaluated who underwent either distal pancreatectomy or pancreaticoduodenectomy and the primary end point developed in 13.3%. We instituted a program of routine pasireotide administration after its efficacy in reducing these complications was demonstrated in a randomized, placebo-controlled study conducted at our center in 2014. This trial reported a statistically significant absolute risk reduction of 11.7% in those receiving pasireotide, but we have not reported the impact of pasireotide in routine use outside of a trial setting. For the current study, the placebo group for the earlier trial served as a historical comparison group, as the setting and outcomes measures are identical. During the nearly 3-year period examined for this study, an absolute risk reduction of 7.6% was observed. Although the overall incidence of fistula or abscess formation was higher than the incidence observed in those patients receiving pasireotide in the trial setting (9.2%), the decrease shown here remained significantly lower than the earlier placebo cohort. In addition, this occurred despite the current study group having more cases at high risk for pancreatic leakage (coexisting soft gland/small duct) compared with the placebo group (Table 2). The current group also had more comorbidities than the placebo group, as evidenced by higher ASA scores.

Postoperative pancreatic leak and related complications are a major source of postoperative morbidity and continue to defy innumerable attempts at mitigation.[1,3] Interest in a pharmacologic solution using somatostatin analogues has been longstanding, with octreotide being intensively studied during the past 3 decades.[10,13,14] Because meta-analyses have suggested the efficacy of octreotide is limited, its routine use is not widespread[12,23] at most institutions. However, notable exceptions exist. In a 2016 study, >80% of German surgeons reported using somatostatin analogues either some or all of the time after pancreatectomy, although only 5% of these included pasireotide.[23] Pasireotide has different pharmacologic properties, with a broader binding profile and longer half-life compared with octreotide and, because of this, we initiated a randomized placebo-controlled trial. Using the risk reduction data from that trial, 3 articles (including 1 from our group) suggested routine pasireotide use would be cost-effective or cost-neutral[24-26]; a fourth article has suggested costs would be further optimized if pasireotide was limited to those at highest risk for fistula.[27] Due to the efficacy results from our trial and these data about cost, we implemented a standard practice of giving perioperative pasireotide after all pancreatic resections at MSKCC.

In early 2018, two similar studies first reported the effects of pasireotide at institutions beyond MSKCC. Elliot and colleagues[19] at the University of California-Los Angeles gave pasireotide to 111 consecutive patients and compared the rate of clinically relevant pancreatic fistula with 168 historical controls; no difference in fistula prevalence was noted.[19] At Washington University, Dominguez-Rosado and colleagues[18] conducted a similar study with 127 consecutive patients receiving pasireotide compared with pre- and post-pasireotide cohorts that did not receive the drug and similarly failed to demonstrate a significant reduction in overall or clinically relevant fistula incidence. A subgroup of 112 patients was propensity-matched due to considerable differences in patients who did or did not receive pasireotide with similar findings. Although the results of these 2 studies appear to conflict with the data reported here, several important differences exist. All define pancreatic fistula as persistent amylase-rich drainage after operation, approximating the consensus definition favored

by the ISGPS, but the primary outcomes measure differs. In the current study, and original randomized trial, the primary end point aggregates pancreatic leakage and intra-abdominal abscesses, and the University of California-Los Angeles study adheres to ISGPS grade B/C events only and the Washington University study favors severe morbidity classified by a modified accordion grading system. These differences magnify the dissimilar baseline event rate seen between the studies. Although the MSKCC Surgical Secondary Events morbidity reporting system (shown in Table 1) does not replicate the ISGPS definitions when evaluating pancreatic leak/fistula, our primary end point of Grade 3 events of higher essentially mirrors grade B/C events from the ISGPS—so-called "clinically relevant" postoperative pancreatic fistulas. Also, important disparities exist in the study samples and institutional practice patterns. For example, in the Washington University study, 95% of those who received pasireotide received operative drains, compared with 25% of patients in the current study. Defining a grade B leak in the setting of an operative drain has some subjectivity, as it is determined not only by the presence of amylase in the drain but also by a "clinically relevant condition" related to the fistula. Although some could suggest simply having any drain for 10 days would be clinically significant, others might consider that a biochemical leak only and a grade A fistula. This emphasizes the importance of randomization and blinded assessment. The impact of these differences might explain the differential findings between our studies, but the data here clearly demonstrate a durable reduction in pancreatic leaks, fistulas, and intra-abdominal abscesses at our institution during the 3-year study period in more than 650 patients undergoing pancreatic resection.

Reductions in biliary leak/fistula and postoperative hemorrhage were notable findings in the analysis of secondary outcomes. Large historical databases suggest biliary leaks complicate approximately 3% of pancreaticoduodenectomies.[2,20] In this study, biliary leakage developed in only 4 patients (0.6%, or 0.9% when limited to those undergoing pancreaticoduodenectomy). The known decrease in bile secretion after administration of somatostatin analogues might be the physiologic rationale for this observed decrease. The rate of grade 2 or higher (requiring transfusion) postoperative hemorrhage also decreased by nearly half among those who received pasireotide (8.8% to 4.6%), a trend that neared statistical significance ($p = 0.07$). Interestingly, the group from Washington University reported a decrease in postoperative anemia or hemorrhage of an even greater magnitude in their study; this was statistically significant in their analysis. In addition, the decrease persisted in the propensity-matched subgroup analysis as well.[18] This decrease might be due to a reduction in extraluminal late post-pancreatectomy hemorrhage secondary to concomitant reduction in pancreatic leak—or fistula-mediated vascular erosion and bleeding, a phenomenon well-known to pancreatic surgeons. Alternatively, somatostatin-mediated decreases in portal and splanchnic blood flow can be causative. These findings merit additional study as outcomes independent of pancreatic leakage in any future trials examining pasireotide after pancreatectomy.

Pasireotide remains a routine component of pancreatic resection at our institution. Although the price of its use is not inconsequential, the lasting decrease in fistula, leak, and abscess formation shown here supports the cost-effectiveness models of previous reports from our center.[24-26] Nausea remains the most prominent treatment-related toxicity and is treatment-limiting in approximately 15% of patients. During the study period, we noted a significant improvement in pasireotide tolerance when co-administered with parenteral ondansetron, which mitigates severe nausea in many of our patients. Intriguingly, no difference in event rate was observed in the study population that received partial (fewer than 14) dose regimens. This suggests the duration of administration could possibly be reduced without loss of effect and a potential cost savings.

As in the studies from Washington University and University of California-Los Angeles, this study is limited by its retrospective nature, even though data on morbidity were collected prospectively. In addition, despite a large number of patients during a prolonged period, this remains a single-center study and confirmatory of practices tested in a clinical trial at our institution. The placebo-receiving comparison population was smaller than the study population that received pasireotide; however, this was considered preferable to an "historical" group of larger size, given the careful evaluation of outcomes and granular data available for participants in the pasireotide clinical trial. Despite interesting secondary findings (ie reduction in hemorrhage), the role of pasireotide in conclusively reducing leak-related complications after pancreatectomy at other institutions remains unconfirmed. It has been suggested that the lack of efficacy of somatostatin analogues might be due to their inability to act on a "stunned" pancreas in a postoperative state,[28] but this is contradicted by the available physiologic data. Studies have consistently shown a decrease in volume and potency of pancreatic exocrine secretions with somatostatin analogue therapy, with the mean maximum drain amylase concentration with pasireotide in the Washington University study being reduced 60% to 70% compared with untreated patients.[7,18] It seems that the exocrine function of the postoperative pancreas is undoubtedly affected by somatostatin analogues, but translation of this effect into reducing clinically relevant morbidity after pancreatectomy appears

different between institutions and available studies. The etiology of this phenomenon remains unclear. Certainly, any future studies examining pasireotide should be multi-institutional and ideally stratified by variables, such as duct size and operative drain, to maximize their impact. Such a multi-institutional trial would serve to conclusively address the lack of uniformity seen among the single-institution studies currently available.

CONCLUSIONS

After 3 years of routinely administering pasireotide to all patients undergoing pancreatic resection, we have found the aggregate incidence of clinically relevant pancreatic leakage, fistula, and abscess formation to be 13.3%, a significant decrease from those not receiving pasireotide in our previous study population. Incidence of biliary leaks and postoperative hemorrhage has also decreased. We continue to use pasireotide routinely in the perioperative care of patients undergoing pancreatectomy.

Author Contributions

Study conception and design: Kunstman, Goldman, Allen

Acquisition of data: Kunstman, Balachandran, D'Angelica, Kingham, Jarnagin, Allen

Analysis and interpretation of data: Kunstman, Goldman, Gönen, Allen

Drafting of manuscript: Kunstman, Allen

Critical revision: Kunstman, Goldman, Balachandran, D'Angelica, Kingham, Jarnagin, Allen

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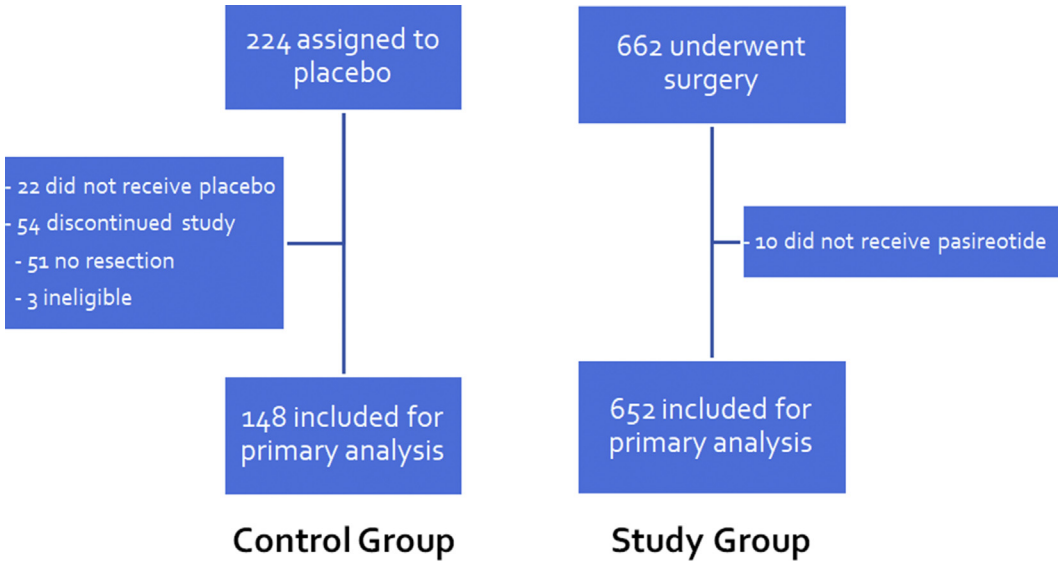

eFigure 1. Schematic of study design noting enrollment and randomization from earlier controlled trial evaluating pasireotide in patients undergoing pancreatectomy[17] compared with the current study, as indicated.

eTable 1. Multivariable Logistic Regression Analysis of Risk Factors for the Primary End Point (Aggregate Incidence of Pancreatic Fistula/Leak/Abscess) Across All Study Participants (n = 800)

	Multivariable analysis		
Characteristic	**Odds ratio**	**95% CI**	**p Value**
Treatment cohort			0.13
Pasireotide	0.65	0.38–1.13	
Placebo	ref	—	—
Age at surgery, y	0.98	0.97–1.00	0.10
BMI, kg/m^2	1.04	1.00–1.08	0.049*
American Society of Anesthesiologists score			0.59
1–2	ref	—	—
3	1.31	0.78–2.17	
4	1.16	0.30–4.42	
Sex			0.13
Female	1.39	0.91–2.14	
Male	ref	—	—
Resection			0.67
Distal pancreatectomy	0.90	0.56–1.45	
Whipple	ref	—	—
Gland texture			0.035*
Soft	1.67	1.04–2.71	
Firm	ref	—	—

Due to covariance with gland texture, pancreatic duct size could not be included in the final model.
*Significant.
ref, reference statistics.

eTable 2. Test of Interaction for Pasireotide- vs Placebo-Receiving Cohorts with Known Risk Factors for the Primary End Point

Pasireotide vs placebo comparison	Odds ratio	95% CI	p Value
Duct size			
>4 mm	0.63	0.30–1.32	0.74
≤4 mm	0.53	0.30–0.95	—
Gland texture			
Firm	0.36	0.18–0.73	0.12
Soft	0.77	0.41–1.43	—
Resection type			
Whipple	0.66	0.37–1.16	0.46
Distal pancreatectomy	0.46	0.21–0.99	—
Risk profile			
High (≤4 mm *and* soft)	0.40	0.31–1.29	—
Moderate (≤4 mm *or* soft)	0.65	0.28–1.49	0.69
Low (>4 mm duct, firm)	0.63	0.16–1.01	—

No subgroup was identified that demonstrated a change in risk of primary end point.