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Prophylactic octreotide for postoperative pancreatic fistula in patients with pancreatoduodenectomy

Risk-stratified analysis

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Abstract

Background: Postoperative pancreatic fistula is one of the most critical complications following pancreatic surgery. This study aimed to evaluate the utility of selective prophylactic octreotide for patients at high risk of developing postoperative pancreatic fistula.

Methods: From June 2019 to July 2020, 263 patients underwent pancreatoduodenectomy with pancreatojejunostomy at Samsung Medical Center. The individual fistula risk scores were calculated using a previously developed nomogram. The clinicopathological data of the patients were retrospectively reviewed.

Results: There were 81 patients in the low-risk group and 182 patients in the high-risk group. No statistically significant differences were found in the rates of clinically relevant postoperative pancreatic fistula between octreotide group and the control group in all patients (15.0% vs 14.7%, $P = .963$) and in the high-risk group (16.1% vs 23.6%, $P = .206$). In risk factor analysis, postoperative octreotide was not an independent risk factor for clinically relevant pancreatic fistula in all patients and the high-risk group. Drain fluid amylase levels on the first postoperative day were significantly associated with clinically relevant postoperative pancreatic fistula, regardless of the individual risk.

Conclusions: The selective use of octreotide, even in high-risk patients, showed no protective effect against pancreatic fistula. Therefore, the routine use of postoperative octreotide is not recommended.

Abbreviations: ASA = American Society of Anesthesiology, BMI = body mass index, CI = confidence interval, CR-POPF = clinically relevant POPF, CT = computed tomography, DFA = drain fluid amylase, DP = distal pancreatectomy, ISGPF = International Study Group of Pancreatic Fistula, MPD = main pancreatic duct, MRCP = magnetic resonance cholangiopancreatography, OR = odds ratio, PD = pancreatoduodenectomy, POD = postoperative day, POPF = postoperative pancreatic fistula.

Keywords: octreotide, pancreatoduodenectomy, postoperative pancreatic fistula, somatostatin analog

1. Introduction

Pancreatoduodenectomy (PD) is a complex surgical procedure performed in patients with periampullary tumors, with the morbidity rate reported up to 40% even at high-volume centers.[1] One of the most fatal complications is postoperative pancreatic fistula (POPF), which increases other morbidities such as intra-abdominal hemorrhage and infection.[2,3] Clinically relevant postoperative pancreatic fistula (CR-POPF) defined by the International Study Group of Pancreatic Fistula (ISGPF)[4]

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is related to major morbidity, mortality, and poor overall survival by delaying adjuvant treatment.[3]

It is still debatable whether the routine prophylactic use of somatostatin analogs such as octreotide could reduce the incidence of POPF.[5–15] The potential protective effect of somatostatin analogs on POPF was based on its pharmacological mechanism, which inhibits the exocrine secretions of pancreas.[12] The 2013 Cochrane Review recommended routine somatostatin analogs use after pancreatic surgery considering its lack of serious adverse effects and low cost.[7] However, the role of octreotide in preventing POPF following PD was not supported in a meta-analysis of previous randomized controlled trials.[12] Pasireotide, another type of somatostatin analog, was reported to be effective for decreasing POPF or intra-abdominal abscesses in a randomized trial,[8] while another prospective study failed to validate the efficacy of pasireotide in preventing POPF.[13]

There have been many attempts to predict the risk of POPF in patients undergoing PD and several platforms have been invented.[16–18] We invented a web-based nomogram for predicting CR-POPF following PD[19] and it has been used to select patients at high risk for CR-POPF in our institution. To the best of our knowledge, there is no study investigating the effectiveness of prophylactic somatostatin analogs for patients with high-risk of POPF. Therefore, this study aimed to investigate the efficacy of prophylactic octreotide selectively administered in high-risk patients.

2. Materials and methods

2.1. Patient database

Patients who underwent PD at Samsung Medical Center from June 2019 to July 2020 were included in the study. The prospectively collected data of the patients including demographic information, pre-operative laboratory and imaging tests, pathology reports, and surgical outcomes were retrospectively reviewed. Patients in whom pancreatico-enteric anastomosis was not performed due to any reasons, including unintended total pancreatectomy, were excluded. Finally, a total of 263 patients were included in the analysis. The study was approved by the Institutional Review Board of Samsung Medical Center (Seoul, Korea, approval no. 2020-09-122). Our Institutional Review Board of Samsung Medical Center waived the need for written informed consent from the participants since the research involved minimal risk to subjects, and there was no reason to assume rejection. All methods for the study were performed in accordance with the relevant guidelines and regulations.

2.2. Preoperative data and risk stratification

The individual risk for CR-POPF was calculated using the previously developed nomogram-based web calculator, which is available at http://popf.smchbp.org.[19] Six preoperative variables in the calculation included gender, body mass index (BMI), the American Society of Anesthesiology (ASA) physical classification score, serum albumin, tumor location, and the diameter of the main pancreatic duct (MPD) measured on computed tomography (CT) or magnetic resonance cholangiopancreatography (MRCP). According to their scores, the patients were classified as low-risk ($<$ 25%) or high-risk ($\geq$25%).

According to our guidelines, all patients in the high-risk group were supposed to receive octreotide, but the treatment was finally determined at the surgeons' discretion. Patients with reported adverse drug reactions to octreotide were assigned to the control group.

2.3. Postoperative outcomes

Attending physicians who were involved in the post-operative management of the patients reviewed all surgical outcomes including POPF based on the medical records. The Clavien-Dindo classification was used for grading in-hospital complications. POPF was diagnosed when the amylase level of the drain fluid (DFA) was greater than three times the upper normal serum value and classified according to the 2016 ISGPF definition and grading.[4] The length of hospital stay and the rate of readmission within 90 days after discharge were investigated.

2.4. Statistical analysis

Comparison of the clinical characteristics and surgical outcomes between the groups of patients was performed using the Student's t-test and Chi-squared test. Binary logistic regression was used to predict risk factors and to identify if prophylactic octreotide would be an independent factor for CR-POPF. The odds ratios (ORs) were reported with 95% confidence intervals (CIs). Variables with p-values of less than 0.05 were regarded as statistically significant. All statistical analyses were performed using IBM SPSS software (version 26, SPSS Inc., Chicago, IL, USA).

3. Results

Among 263 patients, 81 patients were in the low-risk group and 182 patients were in the high-risk group. Table 1 shows a comparison of the demographic, clinical characteristics and surgical outcomes between the two groups. The mean BMI was higher in the high-risk group than in the low-risk group (22.2 vs 24.3, $P < .001$). More patients in the high-risk group had preoperative endoscopic biliary drainage (37.0% vs 52.2%, $P = .023$). The mean MPD size estimated from preoperative images was larger in the low-risk group than in the high-risk group (4.9 vs 3.3, $P < .001$). In terms of intraoperative findings, there were more patients with gross pancreatitis and hard pancreatic texture in the low-risk group than in the high-risk group (51.9% vs 29.4%, $P = .001$; 40.7% vs 14.5%, $P < .001$, respectively). Pancreatic tumors were more common with the patients in the low-risk group than in the high-risk group (84.0% vs 40.1%, $P < .001$).

Fourteen (17.3%) patients in the low-risk group and 93 (51.1%) patients in the high-risk group received postoperative octreotide for more than three days ($P < .001$). More patients in the low-risk group had a postoperative day (POD) 1 DFA of less than 5000 IU/L comparing to the patients in the high-risk group (85.2% vs 70.3%, $P = .010$). In the high-risk group, the rates of CR-POPF and overall complications were higher than in the low-risk group (3.7% vs 19.8%, $P = .001$; 42.0% vs 57.1%, $P = .023$, respectively). However, the complications more severe than Clavien-Dindo classification grade III were comparable.

Comparisons between the octreotide group and the control group are shown in Table 2. In the comparisons including all patients, more patients had a higher BMI in the octreotide group than in the control group (24.2 vs 23.3, $P = .001$). The octreotide group had fewer patients with pancreatic tumors than the

Table 1

Comparisons of demographics, clinical characteristics, and surgical outcomes between the low-risk and high-risk groups (n = 263).

Variables	Low-risk group <25% (n = 81)	High-risk group ≥ 25% (n = 182)	*P*
Age	65.6 (±10.2)	64.8 (±10.2)	0.518
Sex			0.109
Male	39 (48.1%)	107 (58.8%)	
Female	42 (51.9%)	75 (41.2%)	
BMI (kg/m^2), mean	22.2 (±2.5)	24.3 (±2.9)	<0.001
ASA score			0.382
I	5 (6.2%)	13 (7.1%)	
II	65 (80.2%)	132 (72.5%)	
III	11 (13.6%)	37 (20.3%)	
Pre-op serum albumin (g/dL), mean	4.0 (±0.4)	4.1 (±0.4)	0.487
Pre-op endoscopic biliary drainage, Yes	30 (37.0%)	95 (52.2%)	0.023
Estimated MPD size (mm), mean	4.9 (±2.5)	3.3 (±1.6)	<0.001
Operation time (min), mean	316.4 (±65.0)	318.0 (±63.9)	0.860
Intra-op pancreatitis, Yes	40 (51.9%)	50 (29.4%)	0.001
Intra-op pancreatic texture*			<0.001
Soft	24 (29.6%)	90 (50.3%)	
Moderate	24 (29.6%)	63 (35.2%)	
Hard	33 (40.7%)	26 (14.5%)	
Intra-op transfusion, Yes	7 (8.6%)	7 (3.8%)	0.137
Tumor location			<0.001
Pancreatic tumors	68 (84.0%)	73 (40.1%)	
Others†	13 (16.0%)	109 (59.9%)	
Post-op octreotide			<0.001
No	67 (82.7%)	89 (48.9%)	
Yes	14 (17.3%)	93 (51.1%)	
POD1 DFA			0.010
<5000IU	69 (85.2%)	128 (70.3%)	
≥ 5000IU	12 (14.8%)	54 (29.7%)	
POPF			
No	55 (67.9%)	58 (31.9%)	<0.001
BCL	23 (28.4%)	88 (48.4%)	<0.001
CR-POPF	3 (3.7%)	36 (19.8%)	0.001
Overall complications	34 (42.0%)	104 (57.1%)	0.023
CD grade ≥ 3 complications	11 (13.6%)	44 (24.2%)	0.051
Length of stay (days), mean	10.7 (±4.8)	12.4 (±7.3)	0.029
Re-admission	10 (12.3%)	25 (13.7%)	0.759

ASA = American Society of Anesthesiologists, BMI = body mass index, CD = Clavien-Dindo, CR-POPF = clinically relevant POPF, DFA = drain fluid amylase, Intra-op = intraoperative, MPD = main pancreatic duct, POD1 = the first postoperative day, POPF = postoperative pancreatic fistula, Post-op = postoperative, Pre-op = preoperative.

* three patients had no information on intraoperative pancreatic texture.

† includes bile duct cancer, duodenal cancer and Ampulla of Vater cancer.

control group (40.2% vs 62.8%, $P < .001$). The rate of POPF was higher in the octreotide group but the rate of CR-POPF did not differ significantly (15.0% vs 14.7%, $P = .963$).

We performed a separate analysis of the patients in the high-risk group (Table 2). There were no statistically significant differences in the preoperative factors between the two groups. More patients in the octreotide group had a soft pancreas than in the control group (60.4% vs 39.8%, $P = .021$). Pancreatic tumors were more common in the control group (32.3% vs 48.3%, $P = .027$). The surgical outcomes including the rates of CR-POPF did not differ significantly between the two groups.

In the risk factor analysis for CR-POPF including all patients (Table 3), MPD size, soft pancreas, pancreatic tumors, and POD1 DFA ≥ 5000 IU/L were associated with CR-POPF in the univariable analysis. In the multivariable analysis, MPD size (OR = 0.738, 95% CI: 0.572–0.951, $P = .019$) and POD1 DFA ≥ 5000 IU/L (OR = 3.519, 95% CI: 1.698–7.294, $P = .001$) were independent risk factors of CR-POPF. However, postoperative octreotide was not related to CR-POPF in either univariable or multivariable analysis. In the analysis of only high-risk patients (Table 4), POD1 DFA ≥ 5000 IU/L significantly increased CR-POPF in the multivariable analysis (OR = 2.661, 95% CI: 1.221–5.799, $P = .014$) but postoperative octreotide was not associated with CR-POPF.

4. Discussion

In our study, there was no statistically significant difference in the incidence of CR-POPF between patients in the octreotide group and the control group. Postoperative octreotide was not associated with CR-POPF, consistent with the findings of several previous studies.[5,9,12–15] Schorn et al.[15] performed a subgroup analysis of the types of pancreatic resections in a recent meta-analysis and identified that somatostatin analogs did not affect CR-POPF after PD but might be associated with less POPF after distal pancreatectomy (DP). This can be explained by the key mechanism of somatostatin analogs, which decreases the production of pancreatic juice. After DP, patients with an altered function of the sphincter of Oddi and stasis of pancreatic juice may benefit from the drug.[20] Another meta-analysis found

Table 2

Comparison of demographics, clinical characteristics, and surgical outcomes between the octreotide and control groups in all patients (n = 263) and the high-risk group (n = 182).

Variables	All patients (n = 263)			High-risk group (n = 182)		
	Octreotide group (n = 107)	Control group (n = 156)	*P*	Octreotide group (n = 93)	Control group (n = 89)	*P*
Clinical factors						
Age	66.2 (±8.4)	64.2 (±11.2)	.104	65.8 (8.5)	63.8 (±11.7)	.189
Sex			.879			.268
Male	60 (56.1%)	86 (55.1%)		51 (54.8%)	56 (62.9%)	
Female	47 (43.9%)	70 (44.9%)		42 (45.2%)	33 (37.1%)	
BMI (kg/m^2), mean	24.2 (±2.6)	23.3 (±3.1)	.010	24.3 (±2.6)	24.3 (±3.1)	.877
ASA score			.086			.099
I	3 (2.8%)	15 (9.6%)		3 (3.2%)	10 (11.2%)	
II	82 (76.6%)	115 (73.7%)		69 (74.2%)	63 (70.8%)	
III	22 (20.6%)	26 (16.7%)		21 (22.6%)	16 (18.0%)	
Pre-op serum albumin	4.1 (±0.4)	4.0 (±0.4)	.950	4.1 (±0.4)	4.1 (±0.4)	.785
Pre-op endoscopic biliary drainage, Yes	57 (53.3%)	68 (43.6%)	.122	52 (55.3%)	44 (48.9%)	.383
Estimated MPD size (mm), mean	3.5 (±1.8)	4.0 (±2.1)	.087	3.2 (±1.5)	3.4 (±1.7)	.495
Operation time (min), mean	318.8 (±64.0)	316.6 (±64.3)	.780	317.9 (±64.4)	318.0 (±63.7)	.992
Intra-op pancreatitis, Yes	31 (31.0%)	59 (40.1%)	.143	24 (27.9%)	26 (31.0%)	.663
Intra-op pancreas texture*			.009			.021
Soft	58 (55.2%)	56 (36.1%)		55 (60.4%)	35 (39.8%)	
Moderate	29 (27.6%)	58 (37.4%)		26 (28.6%)	37 (42.0%)	
Hard	18 (17.1%)	41 (26.5%)		10 (11.0%)	16 (18.2%)	
Intra-op transfusion, Yes	6 (5.6%)	8 (5.1%)	.865	5 (5.4%)	2 (2.2%)	.445
Tumor location			<.001			.027
Pancreatic tumor	43 (40.2%)	98 (62.8%)		30 (32.3%)	43 (48.3%)	
Others†	62 (59.8%)	58 (37.2%)		63 (67.7%)	46 (51.7%)	
Surgical outcomes						
POD1 DFA			.230			.648
<5000IU	76 (71.0%)	121 (77.6%)		64 (68.8%)	64 (71.9%)	
≥ 5000IU	31 (29.0%)	35 (22.4%)		29 (31.2%)	25 (28.1%)	
POPF			.011			
No	36 (33.6%)	77 (49.4%)		27 (29.0%)	31 (34.8%)	.401
BCL	55 (51.4%)	56 (35.9%)	.033	51 (54.8%)	37 (41.6%)	.152
CR-POPF	16 (15.0%)	23 (14.7%)	.963	15 (16.1%)	21 (23.6%)	.206
Overall complications	56 (52.3%)	82 (52.6%)	.803	50 (53.8%)	54 (60.7%)	.346
CD grade ≥ 3 complications	22 (20.6%)	33 (21.2%)	.908	20 (21.5%)	24 (27.0%)	.390
Length of Stay (days), mean	12.0 (±6.8)	11.8 (±6.7)	.814	12.3 (±7.2)	12.6 (±7.6)	.782
Re-admission	14 (13.1%)	21 (13.5%)	.929	12 (12.9%)	13 (14.6%)	.739

ASA = American Society of Anesthesiologists, BMI = body mass index, CD = Clavien-Dindo, CR-POPF = clinically relevant POPF, DFA = drain fluid amylase, Intra-op = intraoperative, MPD = main pancreatic duct, POD1 = the first postoperative day, POPF = postoperative pancreatic fistula, Pre-op = preoperative.

* three patients had no information on intraoperative pancreatic texture.

† includes bile duct cancer, duodenal cancer and Ampulla of Vater cancer.

that prophylactic octreotide had no benefit in reducing POPF[12] and that octreotide might be related to unexpected adverse outcomes, such as a delay in healing at the anastomoses in postoperative patients since it causes a reduction in splanchnic blood flow.[21]

In contrast, other studies have reported the benefits of somatostatin analogs in reducing POPF.[6–8,10,11] It was suggested that octreotide could reduce fistula formation and promote fistula closure by inhibiting exocrine pancreatic secretion and hardening pancreatic tissue to stabilize anastomosis.[11,22] This led to significant improvements in other clinical outcomes such as shorter hospital duration and no increased hospital costs.[23] Some authors also emphasized that octreotide is a well-tolerated drug with few side effects.[6,7] Pasireotide reduced the risk of CR-POPF, postoperative leakage, and abscesses, and these reductions were significant in patients with a dilated pancreatic duct, according to a single-center randomized controlled study.[8] Another systemic review failed to prove the positive influence of octreotide but found that pasireotide, with a longer half-life and broader binding profile, might have a potential role in reducing POPF.[10]

In this regard, a series of studies have reported inconsistent results, making it difficult to measure the efficacy of somatostatin analogs for POPF. This may be attributed to the extensive heterogeneity in the study designs. Many studies included patients with all pancreatectomies without risk stratification for POPF, or consideration of the types of resection or anastomosis. Therefore, among patients undergoing PD, we selected those at high risk of CR-POPF using preoperative data and performed subgroup analyses to investigate the efficacy of prophylactic octreotide in the high-risk group. According to our results, the routine administration of octreotide, even for high-risk patients, cannot be recommended.

Another important finding of this study was that a POD1 DFA of more than 5000 IU/L significantly increased CR-POPF in the high-risk group. Several prospective and retrospective studies have supported that POD1 DFA is a strong predictor of POPF, and may be useful for deciding the timing of surgical drain

Table 3

Binary logistic regression analysis for CR-POPF in all patients (n = 263).

	Univariable analysis			Multivariable analysis		
Variable	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Age	0.990	0.957–1.023	.541			
Sex, female (ref. male)	0.847	0.425–1.689	.638			
BMI	1.060	0.946–1.187	.316			
ASA	0.945	0.470–1.901	.873			
Pre-op serum albumin	1.438	0.619–3.344	.398			
Pre-op endoscopic drainage	1.719	0.862–3.428	.124			
MPD size	0.690	0.536–0.888	.004	0.738	0.572–0.951	.019
Intra-op pancreatitis	0.552	0.255–1.193	.552			
Intra-op pancreas texture, soft	2.054	1.028–4.102	.042	1.213	0.564–2.607	.621
Intra-op transfusion	0.955	0.205–4.442	.953			
Pancreatic tumors	0.486	0.242–0.976	.043	0.661	0.312–1.403	.281
POD1 DFA ≥ 5000IU	4.073	2.009–8.257	<.001	3.519	1.698–7.294	.001
Post-op octreotide	1.017	0.509–2.030	.963	0.753	0.351–1.616	.467

BMI = body mass index, CR-POPF = clinically relevant postoperative pancreatic fistula, DFA = drain fluid amylase, Intra-op = intraoperative, MPD = main pancreatic duct, POD1 = the first postoperative day, Pre-op = preoperative.

Table 4

Binary logistic regression analysis for CR-POPF, in the high-risk group (n = 182).

	Univariable analysis			Multivariable analysis		
Variable	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Age	0.986	0.952–1.022	.443			
Sex, female (ref. male)	0.887	0.420–1.871	.752			
BMI	0.966	0.848–1.101	.604			
ASA	0.789	0.381–1.632	.522			
Pre-op albumin	1.925	0.770–4.810	.161			
Pre-op endoscopic drainage	1.818	0.856–3.863	.120			
Intra-op pancreatitis	0.756	0.327–1.750	.514			
Intra-op pancreas texture, soft	1.304	0.625–2.718	.479			
MPD size	0.722	0.536–0.973	.032	0.777	0.573–1.055	.106
Intra-op transfusion	0.667	0.078–5.718	.712			
Pancreatic tumors	0.697	0.324–1.500	.356			
POD1 DFA ≥ 5000IU	3.056	1.438–6.494	.004	2.661	1.221–5.799	.014
Post-op octreotide	0.623	0.298–1.303	.208	0.572	0.264–1.237	.156

BMI = body mass index, CR-POPF = clinically relevant postoperative pancreatic fistula, DFA = drain fluid amylase, Intra-op = intraoperative, MPD = main pancreatic duct, POD1 = the first postoperative day, Pre-op = preoperative.

removal after PD.[24,25] Based on these results, the current Enhanced Recovery After Surgery (ERAS) guidelines for PD recommend early drain removal at postoperative 72 hours in patients with POD1 DFA of < 5000 IU/L.[26] To our knowledge, there is no predictive platform for POPF that includes POD1 DFA and there are limits in predicting POPF with the current known preoperative variables.[27,28] The development of a predictive system including POD1 DFA will be beneficial for re-evaluating the risks of POPF and patient management. Further research is also needed on the potential intrinsic risk factors including the genetic or pathologic characteristics of the patients or diseases.

This study has several limitations. First, because of the lack of randomization, the study is prone to selection bias. The control group of high-risk patients included patients with known adverse drug reactions or no preoperative risk scoring. Other surgeon-specific factors such as the types of reconstruction or the dosages of somatostatin analogs, which may have effects on the development of POPF, were not considered. Above all, the placement and removal of surgical drains, which is now well known to be an important risk factor for POPF, were inconsistent between the surgeons. Second, the validity of the predictive nomogram for POPF has not yet been investigated. Our institution is now planning to validate the accuracy of the platform by external validation. In addition, although the patient's quality of life plays an essential role in treatment, patient-reported outcomes related to drug injections were not evaluated. Despite these limitations, this study included a large number of patients with PD, prospectively stratified according to their POPF risks to investigate the efficacy of the selective use of octreotide.

5. Conclusion

In conclusion, this study identified that prophylactic octreotide after PD did not reduce the incidence of CR-POPF, even in high-risk patients. The findings suggest that the routine use of postoperative octreotide is not recommended. Further prospective studies are needed to identify the patients who may benefit from prophylactic somatostatin analogs.

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Author contributions

So Jeong Yoon: Conceptualization, data curation, formal analysis, methodology, writing–original draft, and writing–review and editing.
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