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Pasireotide administration after pancreaticoduodenectomy may decrease clinically relevant postoperative pancreatic fistula in high-risk patients with small pancreatic ducts, soft pancreatic parenchyma and cystic or neuroendocrine neoplasia

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ABSTRACT

Objectives: Post-operative pancreatic fistula (POPF) is a feared complication after a pancreaticoduodenectomy. Previously in a randomized trial found fewer clinically relevant fistulas (CR-POPF) accompanying administration of perioperative pasireotide. Our hospital previously found that the risk for CR-POPF reached 7% in pancreaticoduodenectomy patients. Here, we aimed to determine the CR-POPF rate accompanying prophylactic pasireotide in patients with a normal pancreas at resection level.

Methods: In this clinical study, perioperative pasireotide was administered to pancreaticoduodenectomy patients treated between 1 July 2014 and 30 April 2016. High-risk individuals were defined preoperatively by the surgeon based on the following: no dilatation of the pancreatic duct, suspected soft pancreas and a cystic or neuroendocrine tumor at the head of the pancreas. If the pancreas was considered hard at surgery, thereby carrying a lower risk for fistula, pasireotide was discontinued following one preoperative 900- μ g dose. Among high-risk patients, pasireotide was continued for one week or until discharge from the hospital.

Results: During the study period, 153/215 pancreatic operations were pancreaticoduodenectomies, 58 (38%) of which were considered high risk for developing clinically significant pancreatic fistula. Among these, 4 (2.6%) developed a grade B or C fistula: 2 in the pasireotide group [3.5%, 95% confidence interval (CI) 0.4–11.9%], 1 in the low-risk group (1.2%, 95% CI 0.0–6.4%; difference: 2.3%, 95% CI -6.4–17.3%) and 1 in the discontinued group (10%).

Conclusion: We found similar rates of CR-POPF among high- and low-risk patients undergoing pancreaticoduodenectomy when using prophylactic perioperative pasireotide in high-risk patients.

Key words: pancreatic surgery, pancreatic fistula, post-operative complications

ABBREVIATIONS

Post-operative pancreatic fistula = POPF

Clinically relevant post-operative pancreatic fistula = CR-POPF

Post-pancreatectomy haemorrhage = PPH

Delayed gastric emptying = DGE

Pancreaticoduodenectomy = PD

Fistula risk score = FRS

Clavien-Dindo = CD

INTRODUCTION

Clinically significant post-operative pancreatic fistula (POPF) is a serious complication following pancreaticoduodenectomy (PD). One of the most widely used definitions for POPF stems from consensus among the International Study Group of Pancreatic Fistula (ISGPF) and its update ^[1,2]. A grade B or C clinically significant fistula (CR-POPF) is defined by a drain amylase level three times higher than the upper normal range on post-operative day

three, including endoscopic, radiologic percutaneous (B) or surgical (C) interventions with organ failure (C) ^[3]. Grade C fistulas carry a mortality risk of 35 % ^[4].

Patients at high-risk of developing CR-POPF typically present with a soft parenchymal texture in the pancreas. If the patient has a so-called hard pancreas, the risk for CR-POPF remains low. Yet, patients with a soft pancreas may be difficult to identify prior to surgery. A neuroendocrine or biliary neoplasm and a narrow pancreatic duct upon preoperative imaging or preserved pancreatic tissue may indicate a high-risk surgery. As such, several risk scores have been suggested, many of which only apply during or after surgery ^[5].

Pasireotide is a somatostatin analogue and binds to four out of five somatostatin receptors. In a randomized trial, Allen et al. ^[6] found that administering pasireotide to all patients undergoing pancreatic surgery lead to half the number of clinically significant grade B or C fistulas. Using pasireotide has not yet become routine in clinical practice given its high price, despite CR-POPF doubling hospital treatment costs compared to the costs of a normal recovery regime. Perhaps, treating all patients with pasireotide would not increase the overall costs given this potential savings ^[7]. Yet, two prospective studies recently found that pasireotide had no effect on postoperative fistula formation or other complications following pancreatic surgery ^[8,9].

In our hospital, the prevalence for B or C fistula previously reached 7% among all patients undergoing pancreatic surgery ^[10]. In this study, we aimed to evaluate the CR-POPF rate in patients at high risk for a fistula when administering prophylactic pasireotide.

MATERIALS AND METHODS

Here, we included all patients undergoing elective PD at the Helsinki University Hospital between July 2014 and April 2016. High-risk individuals were defined preoperatively by the surgeon. There was no dilatation of the pancreatic duct during preoperative imaging and/or there was a signs of normal pancreas. Most preoperative diagnoses indicated something other than ductal adenocarcinoma, suspicion of a mucinous cystic neoplasm or other cystic tumor, neuroendocrine tumor, biliary tract tumors of the intrapancreatic bile duct, neoplasm in the uncinate process of the pancreas or any other condition where the pancreas texture might possibly to be soft. If upon surgery in these patients the pancreas appeared hard according to the operating surgeon and thus carried a lower risk of developing a fistula, the use of pasireotide was discontinued after one preoperative 900- μ g dose. In high-risk patients, pasireotide was continued twice daily for one week or until the patient was discharged from the hospital. During surgery in all of the patients included in this study, pancreaticojejunostomy was performed in the same way: duct-to-mucosa in two layers. The costs for pasireotide (Signifor, Novartis, Basel, Switzerland) were covered by our institution without the involvement of the drug manufacturer.

We collected information on patient age, gender, tumour histology, type of resection and complications from patient files. The postoperative pancreatic fistula rates were first determined based on the original definition from the ISGPF^[3], and were revised according the updated 2016 definition^[4]. Post-pancreatectomy haemorrhage (PPH) and delayed gastric emptying (DGE) were classified according to the ISGPS definitions^[11,12]. Overall complications were categorized according to the Clavien-Dindo classification^[13].

All statistics were calculated using IBM's SPSS version 22. We used the Fisher's exact test or the Kruskal–Wallis test primarily in our analyses, and considered $p < 0.05$ as statistically significant.

The Surgical Department and the Surgical Ethics Committee of Helsinki University Hospital approved the study protocol (D. nro HUS 226/E6/06, extension TMK02 §66 17.4.2013). This study was conducted according to the Helsinki Declaration.

RESULTS

Altogether, 215 patients underwent pancreatic surgery for a suspected tumor between July 2014 and April 2016; 153 of them underwent PD. Among these, 58 (38%) high-risk patients received pasireotide for one week or until discharge from the hospital. In addition, 85 (56%) low risk patients did not receive pasireotide. Pasireotide use was discontinued in 10 (7%) patients based upon findings during surgery, and those patients were excluded from further analysis. Table 1 summarizes the patient demographics.

Among 153 PD patients, we identified a total of 4 (2.6%) CR-POPFs. In the high-risk pasireotide group, there were 2 CR-POPFs (3.4%; 95% CI 0.4–11.9%), 1 CR-POPF in the low-risk group who received no pasireotide (1.2%; 95% CI 0.0–6.4%; difference 2.3%, 95% CI -6.4–17.3%) and 1 CR-POPF for whom pasireotide was discontinued (10%). In the high-risk group, we found more biochemical leaks ($p < 0.001$) than in the low-risk group, although the difference in CR-POPF between the high- and low-risk groups was not significant (Table 2). In addition, we found no significant difference in DGE or PPH between groups (Table 3).

High-risk patients had more overall complications [CD classification grades 1–5, 51 (88%) vs. 53 (62%) for high- and low-risk patients, respectively, $p = 0.001$; Table 4]. In total, 22 (15%) patients had CD grade 3–5 complications: 12 (21%) in the high-risk group and 10 (12%) in low-risk group ($p = 0.163$).

DISCUSSION

After selective perioperative use of pasireotide in pancreaticoduodenectomy patients the number of CR-POPF in high-risk patients appeared to be close to that among low-risk patients in our study. Through perioperative pasireotide use in high-risk patients, the overall CR-POPF rate declined in our hospital from 7% during the period 2000 to 2013 to 2.6% during our study^[10]. This reduction in the CR-POPF rate was larger than that seen in a randomized study by Allen et al.^[6] where the CR-POPF rate was reduced to half. The discrepancy may stem in part from the patient selection in this study, but may also result from the development of patient care in general compared to care available during the early 2000s. In 2012 and 2013, the clinically relevant surgical fistula rate in our hospital reached 9.4%, and therefore changing the study setting the difference in fistula rates would be same or higher. Unfortunately it is not possible to reliably assess specifically high-risk patients retrospectively.

Two recent prospective studies published suggest that pasireotide carries no clinical value on reducing CR-POPF. Elliot et al.'s^[8] study included no subgroup analyses of patients with a high risk of fistula formation or separate analyses of PD patients with complete pasireotide treatment. In the other study, Young et al^[9] used a validated Fistula Risk Score (FRS) system to identify high-risk individuals. They found an overall CR-POPF rate that was quite high (32.2%) among PD patients.

Several scores for predicting the risk of CR-POPF have been described^[7,14]. However, most are not preoperative. In our study, 10 (6.5%) patients were preoperatively incorrectly identified as high-risk patients. Unfortunately, we could not fully determine the FRS in this analysis since the actual main pancreatic duct diameter was not routinely recorded during surgery.

The cost analysis from a randomized study found that the use of pasireotide in all patients did not increase the overall treatment costs, since treating each CR-POPF case is costly, thus cancelling out the high price of the drug ^[6]. The treatment of CR-POPF requires computed tomographies, the placement of percutaneous drains, re-operations, intensive care, antimicrobial treatment and extended hospital stays. In a randomized study, the costs of treatment among the placebo group did not significantly differ from that of the pasireotide group. Our results indicate that it could be effective to use perioperative pasireotide in high-risk patients to lower the fistula risk. The total costs associated with administering perioperative pasireotide can be reduced when administered to those with a high risk for CR-POPF.

The main outcome of this study was a pancreatic fistula. We analysed all surgical and non-surgical complications, since it may affect patients recovering from the operation. The distribution of CD complications (grade 0–5) was significantly different between high- and low-risk patients ($p = 0.023$; Table 4). High-risk patients including the CR-POPF patients experienced ≥ 3 CD complications, although this difference in complication rates was not statistically significant. Post-operative pancreatitis or other inflammation in the postoperative area might explain the increase in complication rates in high-risk patients. If postoperative fluid collections or abscesses were drained, amylase levels were checked to rule out a fistula. Primarily, complications affected grade 3 patients [6 (7%) vs. 8 (14%)], who underwent ultrasound-guided aspiration of pleural effusion post-operatively. Grade B or C DGE was more common in the high-risk group even though this difference was not significant [7 (8%) vs. 8 (14%)]. The more severe CD grade 4 or 5 complications did not differ between the high- and low-risk groups. Most of the complications occurred during the first post-operative week, with 2 complications (8%; Figs. 1 and 2) occurring more than 30 days after surgery. Typically, 30 days has served as the follow-up period for reporting post-operative

complications, although a longer time frame such as 90 days would be more suitable for use in clinical studies.

Our single-institution study indicates that perioperative pasireotide affects fistula formation in high-risk patients, even though our research material was small and the number of CR-POPF cases remained quite low in the high-risk group as well. Despite previous studies with conflicting results, our findings support Allen et al.'s^[6,8,9] conclusions.

CONCLUSIONS

When perioperative pasireotide was selectively administered to high-risk patients undergoing pancreaticoduodenectomy, the clinically relevant pancreatic fistula rate appeared to approach that among low-risk patients.

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Author(s) have no conflicts of interest to disclosure

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FIGURE LEGENDS

Table 1. Patient demographics (n=143)

*pasi = pasireotide, [†]ASA = American Society of Anesthesiologists, [‡]d=day

Table 2. Post-operative pancreatic fistula frequency following pancreaticoduodenectomy.

*pasi = pasireotide, [†]d=day, [‡]POPF = post-operative pancreatic fistula

Table 3. Post-operative delayed gastric emptying, post-pancreatectomy hemorrhage and re-operation frequencies.

*pasi = pasireotide, [†]d=day, [‡]DGE=delayed gastric emptying, [§]PPH=post-pancreatectomy hemorrhage

Table 4. Overall post-operative complication rates following pancreaticoduodenectomy based on the Clavien-Dindo classification

*pasi = pasireotide, [†]d=days, [‡]Clavien-Dindo = CD

Figure 1. Frequency of clinically relevant post-operative pancreatic fistula (CR-POPF)

Figure 2. Frequency of Clavien-Dindo grade 3-5 complications post-operatively

Table 1. Patient demographics (n=143)

	Low-risk, no pasi* (%) n=85	High-risk, pasi* 7 d[‡] (%) n=58	P-value
Gender			
Female	45 (30)	27 (30)	NS
Male	40 (26)	31 (20)	
Age ≥ 65	58 (38)	39 (26)	NS
ASA [†] class 1	3 (2)	1 (1)	NS
ASA [†] class 2	27 (18)	17 (11)	
ASA [†] class 3	47 (15)	35 (23)	
ASA [†] class 4	8 (5)	5 (3)	
Diagnosis			
Pancreatic adenocarcinoma	68 (44)	12 (8)	p<0.001
Other diagnoses	17 (11)	46 (30)	

*pasi = pasireotide, [†]ASA = American Society of Anesthesiologists, [‡]d=day

Table 2. Post-operative pancreatic fistula frequency following pancreaticoduodenectomy.

POPF (grade)	Biochemical leak (%)	B (%)	C (%)
Low-risk (no pasi[*]) n=85	4 (4.7)	0 (0)	1 (1.2)
High-risk (pasi[*] 7 d[†]) n=58	39 (67)	1 (1.7)	1 (1.7)
All n=143	43 (28)	2 (1.3)	2 (1.3)

*pasi = pasireotide, [†]d=day, [‡]POPF = Post-operative pancreatic fistula

Table 3. Post-operative delayed gastric emptying, post-pancreatectomy hemorrhage and re-operation frequencies.

	DGE (B-C) (%)	PPH (B-C) (%)	Re-oper (%)
Low-risk (no pasi) n=85	7 (8)	6 (7)	5 (6)
High-risk (pasi 7 d) n=58	8 (14)	4 (7)	4 (7)
All n=143	15 (10)	10 (7)	9 (6)

pasi = pasireotide, d=day, DGE=delayed gastric emptying, PPH=post-pancreatectomy hemorrhage

Table 4. Overall post-operative complication rates following pancreaticoduodenectomy based on the Clavien-Dindo classification

CD [‡] grade, 90 d [†]	0 (%)	1 (%)	2 (%)	3 (%)	4 (%)	5 (%)
Low-risk (no pasi*) n=85	32 (38)	19 (22)	24 (28)	6 (7)	2 (2.4)	2 (2.4)
High-risk (pasi* 7 d[†]) n=58	7 (12)	21 (36)	18 (31)	8 (14)	3 (5)	1 (1.7)
All n=143	39 (27)	40 (28)	42 (29)	14 (8)	5 (3.5)	3 (2.0)

p=0.023

*pasi = pasireotide, [†]d=days, [‡]Clavien-Dindo = CD

Figure 1. Frequency of clinically relevant post-operative pancreatic fistula (CR-POPF)

Figure 2. Frequency of Clavien-Dindo grade 3-5 complications post-operatively