Clinical Trial/Experimental Study

Medicine®

OPEN

Preventive effects of ulinastatin on complications related to pancreaticoduodenectomy

A Consort-prospective, randomized, double-blind, placebo-controlled trial

Hao Zhang (MD)[a], Chunlu Tan (MD)[a], Xing Wang (MD)[a], Deying Kang (MD)[b], Yonghua Chen (MD)[a], Junjie Xiong (MD)[a], Bole Tian (MD)[a], Kezhou Li (MD)[a], Weiming Hu (MD)[a], Xiaoli Chen (MD)[a], Nengwen Ke (MD)[a], Ang Li (MD)[a], Xubao Liu (MD)[a,*]

Abstract

Postoperative pancreatic fistula (POPF) is one of the most common major complications after pancreaticoduodenectomy (PD). Ulinastatin is an intrinsic trypsin inhibitor and mainly used to treat acute pancreatitis, chronic recurrent pancreatitis, and acute circulatory failure. The study aims to investigate the efficacy of ulinastatin on pancreatic fistula and other complications after PD. This prospective, randomized, double-blind, placebo-controlled trial was conducted in West China Hospital of Sichuan University from December 2012 to December 2014. A total of 106 consecutive patients undergoing PD were randomly assigned to receive ulinastatin or placebo during and after the surgery for 5 days. Baseline clinical characteristics and outcomes of patients were recorded and analyzed. Ninety-two patients including 42 in the ulinastatin group and 50 in the placebo group were available for outcome assessment. The POPF rates were comparable between ulinastatin group (43%) and placebo group (26%), whereas the severe pancreatic fistula rate (grade B+C) was significantly less in ulinastatin group than that in placebo group (7% vs 24%, $P=0.045$). For patients with small pancreatic duct diameter ($\leq$3 mm), ulinastatin could significantly reduce the risk of POPF ($P=0.022$). Ulinastatin had protective effects for patients undergoing PD on the prevention of severe postoperative pancreatic fistula.

Abbreviations: ISGPF = International Study Group of Pancreatic Fistula, PD = Pancreaticoduodenectomy, POPF = Postoperative pancreatic fistula, SD = Standard deviation.

Keywords: pancreaticoduodenectomy, postoperative pancreatic fistula, ulinastatin

1. Introduction

Pancreaticoduodenectomy (PD) is an effective strategy for various malignant and benign diseases of pancreas and periampullary region.[1–5] Along with technical advances, PD has become a surgical procedure with a <5% perioperative death rate.[6–8] Nevertheless, as high as 30% to 50% of patients still suffered from various postoperative complications, such as postoperative pancreatic fistula (POPF), biliary leakage, and delayed gastric emptying.[9–14]

POPF is one of the most common complications after PD with a frequency of 10% to 30%, contributing to the postoperative mortality.[15] A number of surgical strategies, including duct-to-mucosa anastomosis, invagination anastomosis, and other reconstruction routes, have been attempted to prevent POPF.[16,17] But none of them proved sufficiently effective to prevent PF adequately after pancreatectomy. Medicine drugs such as prophylactic octreotide also could not prevent POPF.[18]

Ulinastatin is an intrinsic trypsin inhibitor extracted and purified from human urine that inhibits several enzymes such as alpha-chymotrypsin, lipase, amylase, elastase, and carboxylase.[19] Clinically, ulinastatin is mainly used to treat acute pancreatitis, chronic recurrent pancreatitis, and acute circulatory failure.[20,21] However, the efficacy of ulinastatin on pancreatic fistula after PD has not been investigated.

In this study, we conducted a prospective, randomized, double-blinded, placebo-controlled trial to assess the efficacy of ulinastatin on POPF and other complications after PD.

2. Methods

2.1. Patients

From December 2012 to December 2014, 106 consecutive patients undergoing PD in West China Hospital, Sichuan University, were enrolled in this study. Patients of this study were treated according to the World Medical Association Declaration of Helsinki ethical principles. Informed consents were obtained from all the patients, and the study was approved by the Ethics Committee of West China Hospital, Sichuan University. The study was registered at Chinese Clinical Trial Register (ChiCTR-TRC-12002160).

Patients were recruited according to the following criteria: patients with malignant tumors located in vater ampulla, inferior

Editor: Thomas E. Adrian.

HZ, CT, and XW contributed equally to this work.

The authors report no conflicts of interest.

[a] Department of Pancreatic Surgery, [b] Chinese Evidence-Based Medicine Center, West China Hospital, Sichuan University, Chengdu, P.R. China.

[*] Correspondence: Xubao Liu, Department of Pancreatic Surgery, West China Hospital, Sichuan University No.37 Guoxuexiang, Chengdu 610041, P.R. China (e-mail: xubaoliu16@163.com).

Medicine (2016) 95:24(e3731)

Received: 28 January 2016 / Received in final form: 28 March 2016 / Accepted: 18 April 2016

Published online 1 May 2016

http://dx.doi.org/10.1097/MD.0000000000003731

segment of common bile duct, head of pancreas, or duodenum; patients with benign tumors, such as large inflammatory mass in the head of pancreas, or uncertain properties of mass in the head of pancreas, received PD; patients with colon or stomach cancer invading the head of pancreas or duodenum received PD; age from 18 to 80 years; informed consent.

The exclusion criteria are: patients not suitable for pancreatoduodenectomy confirmed by surgical exploration; patients cannot suffer the operation with serious diseases, such as heart, brain or lung diseases, liver and kidney dysfunction; patients with severe mental illness, including dementia; pregnant or lactating women; patients with allergy or a history of allergic to ulinastatin; participating in other drug experiments in the last 3 months; moribund status.

2.2. Treatment

Enrolled patients were randomized to the double-blind treatment with ulinastatin or placebo before surgery by using a randomly generated number pattern. Standard pancreatoduodenectomy was conducted for each patient in this study. Standard or enlarge lymphadenectomy was chosen according to patient's condition. Some patients underwent pancreatoduodenectomy combined with portal vein resection and reconstruction, when tumor infiltrated the portal vein. A duct-to-mucosa pancreaticojejunostomy was performed for each patient.

Patients in ulinastatin group received 300,000 U of ulinastatin (Guangdong Techpool Bio-pharma Co, Ltd., Guangdong, China) dissolved in 100 mL of 0.9% saline solution and administered by intravenous drip infusion starting just before the surgery for 120 minutes. Then 600,000 U of ulinastatin with 50 mL of 0.9% saline was administered by a 6-hour continuous intravenous infusion with micro pump once daily for 5 consecutive days. Placebo, which had the same character as ulinastatin, with the content of mannitol, Na_2HPO_4, and NaH_2PO_4, was given in the same manner for patients in placebo group. These preparations were performed by independent physicians who were not involved in this study.

2.3. Data collection

Data including medical history, details of the surgical procedure, a surgeon questionnaire (type of resection performed, pancreatic texture, pancreatic duct diameter, bile duct diameter, and etc), pathologic analysis of the resected specimen, and clinical information regarding the postoperative course and complications were collected prospectively on all patients. Data collection was performed by study nurses who were not aware of each patient's group allocation (ulinastatin or control).

2.4. Outcome assessments

Patient outcomes were assessed by physicians and study nurses not aware of the patient's group (ulinastatin or placebo). POPF was defined according to the International Study Group of Pancreatic Fistula (ISGPF), as the amylase concentration of fluid drained out of the abdominal cavity through the catheter after postoperative day 3 is greater than 3 times the serum amylase concentration. The severity of POPF was graded according to the clinical impact on the patients (grades A, B, C) as follows: grade A, without abdominal infection, as "transient fistula," not requiring special treatment; grade B, with abdominal infection or the drainage out of the abdominal cavity sustained >3 weeks, requiring adjustment of the clinical treatment; grade C, severe, life-threatening, need special treatment or surgery. Severe pancreatic fistula was defined as grade B and grade C.

The endpoint of this study was defined as 28-day survival after PD, leaving hospital or death of patients.

2.5. Statistical analysis

Continuous variables were expressed as mean with standard deviation (SD) and compared using Student t test. Categorical data were expressed as number (percentage) and assessed by χ^2 test or Fisher exact test. Logistic regression analysis was used to assess the related factors of POPF. $P<0.05$ indicated a statistically significant difference. All analyses were performed using SPSS software, version 21.0 (SPSS Inc, Chicago, IL).

3. Results

3.1. Baseline characteristics of patients

Of 106 consecutive patients enrolled from December 2012 to December 2014, 14 patients were excluded from analysis, including 8 patients who withdrew participation on their own accord, 5 patients who received ulinastatin using a different drug delivery method, and 1 patient who took other protease inhibitor during the study period. The study population consisted of 92 patients, 42 in the ulinastatin group and 50 in the placebo group (Fig. 1). There were 32 women and 60 men, with a mean age of 57 ± 12 years. The 2 groups were similar with respect to age, sex,

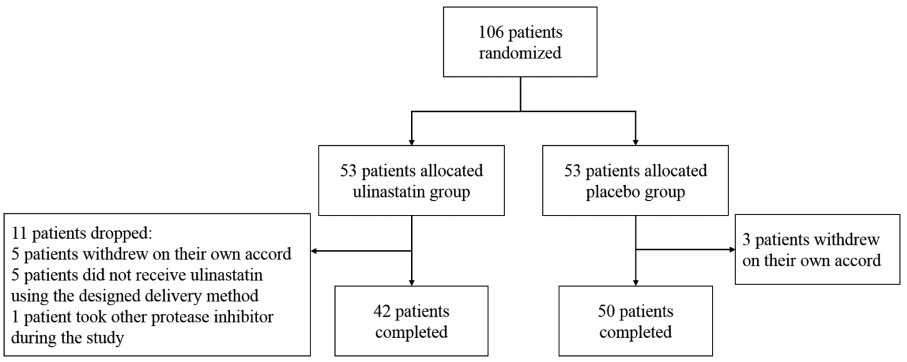

Figure 1. The flow of participant. Of 106 consecutive patients randomized, 14 patients were excluded from analysis. The study population consisted of 92 patients, 42 in the ulinastatin group and 50 in the placebo group.

Table 1

Baseline characteristics and preoperative factors of patients in the trial group and the control group.

	Ulinastatin group (n = 42)	Placebo group (n = 50)	P
Age, y, mean ± SD	56.83 ± 12.20	56.76 ± 11.99	NS
Sex (female)	18 (43%)	14 (28%)	NS
BMI, kg/m^2, mean ± SD	22.10 ± 3.08	22.55 ± 2.49	NS
Preoperative factors			
Hypertension	5 (12%)	7 (14%)	NS
Biliary calculi	8 (19%)	9 (18%)	NS
Gastrointestinal obstruction	3 (7%)	2 (4%)	NS
Peptic ulcer	2 (5%)	1 (2%)	NS
Diabetes mellitus	6 (14%)	4 (8%)	NS
Increased level of serum amylase	11 (26%)	13 (26%)	NS
Anemia	9 (21%)	5 (10%)	NS
Hypoproteinemia	5 (12%)	8 (16%)	NS
Gastrointestinal bleeding	0	1 (2%)	NS
Weight loss			NS
≤5	39 (93%)	41 (82%)	
>5	3 (7%)	9 (18%)	
Jaundice			NS
No	16 (38%)	25 (50%)	
Mild and moderate	15 (36%)	10 (20%)	
Severe	11 (26%)	15 (30%)	
History of smoking	15 (36%)	20 (40%)	NS
History of alcohol intake	12 (29%)	18 (36%)	NS
History of abdominal surgery	14 (33%)	23 (46%)	NS

NS = not significantly different.

Table 2

Intraoperative parameters of patients in the trial group and the control group.

	Ulinastatin group (n = 42)	Placebo group (n = 50)	P
Operative method			NS
Laparotomy	39 (93%)	47 (94%)	
Endoscope	3 (7%)	3 (6%)	
Type of resection			NS
Standard	39 (93%)	46 (92%)	
Pylorus-preserving	3 (7%)	4 (8%)	
Vein resection	5 (12%)	5 (10%)	NS
Lymphadenectomy			NS
Standard	31 (74%)	37 (74%)	
Enlarge	3 (7%)	4 (8%)	
Transfusion	6 (14%)	6 (12%)	NS
Pancreas texture			NS
Soft	20 (48%)	24 (48%)	
Hard	22 (52%)	26 (52%)	
Pancreatic duct diameter, mm			NS
≤3	19 (45%)	25 (50%)	
>3	23 (55%)	25 (50%)	
Bile duct diameter, cm			NS
<1	10 (24%)	19 (38%)	
≥1	32 (76%)	31 (62%)	
Drainage of the pancreatic duct			NS
Internal	20 (48%)	21 (42%)	
External	22 (52%)	29 (58%)	
Operation time, h			NS
<6	29 (69%)	28 (56%)	
≥6	13 (31%)	22 (44%)	

NS = not significantly different.

body mass index, multiple preoperative factors, and history of smoking, alcohol intake, and abdominal surgery (Table 1).

Seventy-two (78%) and 5 (5%) patients underwent an operation for malignant and borderline tumors, respectively. There were no significant differences between the 2 groups with regard to pathology. The most common pathologic findings of the resected specimens were pancreatic adenocarcinoma and periampullary adenocarcinoma, followed by bile duct adenocarcinoma (Table 2).

Most patients received operation through laparotomy, and most patients underwent standard PD (Table 3). Vein resection was performed in 11% of the patients, and lymph node dissection was performed in 82% of the patients. Six (14%) patients in the ulinastatin group and 6 (12%) in the placebo group received transfusion. There were no significant differences between the 2 groups in terms of pancreas texture, pancreatic duct diameter, drainage of the pancreatic duct, and operation time.

3.2. Effects of ulinastatin on prevention of POPF

Patients with PF (grade B and grade B + C) after PD in ulinastatin group were significantly less than those in placebo group ($P = 0.036$; $P = 0.045$, Table 4). No significant differences were observed in other complications between the 2 groups. No adverse reactions to the drugs (ulinastatin and placebo) were observed. Perioperative mortality rate was 1.1% (1/92). The patient died from pulmonary embolism with cardiopulmonary failure.

3.3. POPF related to the poorer outcomes

Presence of POPF in patients who underwent PD was associated with abdominal infection, seroperitoneum, pneumonia, and longer postoperative hospital stay. Hemorrhage and reoperation were overpresented in the patients with POPF, but did not show statistically significant difference ($P = 0.051$, $P = 0.074$). There were no significant differences between patients with POPF and without POPF in biliary leakage, chylous fistula, delayed gastric emptying, intestinal obstruction, wound infection, septicaemia, and multiple organ dysfunction syndrome.

Table 3

Pathologic findings of patients in the trial group and the control group.

	Ulinastatin group (n = 42)	Placebo group (n = 50)	P
Tumor characteristics			NS
Benign	6 (14%)	9 (18%)	
Malignant	35 (83%)	37 (74%)	
Borderline	1 (2%)	4 (8%)	
Pathologic diagnosis			
Pancreatic adenocarcinoma	17 (40%)	19 (38%)	NS
Periampullary adenocarcinoma	10 (24%)	8 (16%)	
Bile duct adenocarcinoma	3 (7%)	8 (16%)	
Chronic pancreatitis	2 (5%)	5 (10%)	
Duodenal adenocarcinoma	4 (10%)	2 (4%)	
Neuroendocrine carcinoma	1 (2%)	2 (4%)	
Pancreatic cystadenoma	2 (5%)	2 (4%)	
Other*	3 (7%)	4 (8%)	

NS = not significantly different.

* Includes solid pseudopapillary neoplasm, intraductal papillary-mucinous neoplasm of the pancreas, periampullary adenosquamous carcinoma, periampullarystromal tumor, autoimmune pancreatitis, and duodenal stromal tumor.

Table 4

Postoperative complications after pancreaticoduodenectomy.

	Ulinastatin group (n = 42)	Placebo group (n = 50)	P
Death	1 (2%)	0	NS
Reoperation	4 (10%)	5 (10%)	NS
Postoperative hospital stay, days, mean ± SD	15 ± 8	13 ± 6	NS
Postoperative pancreatic fistula	18 (43%)	28 (56%)	NS
Grade A	15 (36%)	16 (32%)	NS
Grade B	1 (2%)	8 (16%)	0.036
Grade C	2 (5%)	4 (8%)	NS
Grade B + C	3 (7%)	12 (24%)	0.045
Biliary leakage	1 (2%)	0	NS
Chylous fistula	3 (7%)	0	NS
Hemorrhage	3 (7%)	2 (4%)	NS
Delayed gastric emptying	7 (17%)	5 (10%)	NS
Intestinal obstruction	1 (2%)	1 (2%)	NS
Abdominal infection	7 (17%)	14 (28%)	NS
Wound infection	1 (2%)	3 (6%)	NS
Seroperitoneum	10 (24%)	15 (30%)	NS
Pneumonia	5 (12%)	11 (22%)	NS
Septicemia	2 (5%)	0	NS
Multiple organ dysfunction syndrome	2 (5%)	2 (4%)	NS

NS = not significantly different.

3.4. Risk factors of POPF

In univariate regression analysis, treatment with ulinastatin had no association with the occurrence of POPF ($P = 0.211$; odds ratio [OR]: 0.589, 95% confidence interval [CI]: 0.258–1.348), but was related to severe pancreatic fistula (grade B + C, $P = 0.039$; OR: 0.244, 95% CI: 0.064–0.932), indicating that ulinastatin had protective effects on the prevention of severe POPF for patients undergoing PD.

In patients with PF, 59% had pancreatic duct diameter ≤3 mm, which was significantly higher than that in patients without fistula (37%; $P = 0.037$; Table 5). Ulinastatin could significantly reduce the presence of POPF and grade B POPF in patients with a pancreatic duct diameter ≤3 mm ($P = 0.022$ and $P = 0.029$, respectively, Table 6).

In patients with PF, 57% had soft pancreas, which was comparable with that in patients without fistula (39%; $P = 0.095$; Table 5). Ulinastatin also had some protective effect on POPF and grade B POPF for patients with soft pancreas ($P = 0.083$and $P = 0.053$, respectively; Table 7).

After adjustment for pancreatic duct diameter and pancreas texture, ulinastatin group had a decreased risk of severe pancreatic fistula (grade B + C, $P = 0.043$; OR: 0.246, 95% CI: 0.064–0.955).

4. Discussion

In the current study, the overall incidence of postoperative complications was 71% (65/92). There were 46 patients (50%) with PF after PD in our study, far higher than the numbers reported in previous studies.[22] The reason was that grade A POPF defined in our study was not considered clinically important, and only grade B + C should be counted for the incidence of POPF according to other literatures, which was 16% (15/92). The mild PF was included in our study to comprehensively evaluate the efficacy of ulinastatin for patients who underwent PD. Another important reason might be the different detecting methods of PF. Although using the same definition of

Table 5

Comparison between pancreatic fistula and no pancreatic fistula groups.

	Pancreatic fistula (n = 46)	No fistula (n = 46)	P
Pathologic diagnosis			NS
Pancreatic adenocarcinoma	15 (33%)	21 (46%)	
Periampullary adenocarcinoma	13 (28%)	5 (11%)	
Bile duct adenocarcinoma	4 (9%)	7 (15%)	
Duodenal adenocarcinoma	2 (4%)	4 (9%)	
Chronic pancreatitis	2 (4%)	5 (11%)	
Neuroendocrine carcinoma	3 (7%)	0	
Pancreatic cystadenoma	1 (2%)	3 (7%)	
Pancreatic duct diameter, mm			0.037
≤3	27 (59%)	17 (37%)	
>3	19 (41%)	29 (63%)	
Pancreas texture			0.095
Soft	26 (57%)	18 (39%)	
Hard	20 (43%)	28 (61%)	
Postoperative factors			
Biliary leakage	0	1 (2%)	NS
Chylous fistula	0	3 (7%)	NS
Hemorrhage	5 (11%)	0	0.051
Delayed gastric emptying	4 (9%)	8 (17%)	NS
Intestinal obstruction	0	2 (4%)	NS
Abdominal infection	16 (35%)	5 (11%)	0.006
Wound infection	3 (7%)	1 (2%)	NS
Seroperitoneum	18 (39%)	7 (15%)	0.010
Pneumonia	14 (30%)	2 (4%)	0.001
Septicemia	2 (4%)	0	NS
Multiple organ dysfunction syndrome	4 (9%)	0	NS
Reoperation	7 (15%)	2 (4%)	0.074
Postoperative hospital stay, days, mean ± SD	16 ± 7	12 ± 6	0.002

NS = not significantly different.

Table 6

Pancreatic fistula and pancreatic duct diameter.

	Ulinastatin group	Placebo gr oup	P
Pancreatic duct diameter ≤3 mm	n = 19	n = 25	
Postoperative pancreatic fistula	8 (42%)	19 (76%)	0.022
Grade A	6 (32%)	11 (44%)	NS
Grade B	0	6 (24%)	0.029
Grade C	2 (11%)	2 (8%)	NS
Grade B + C	2 (11%)	8 (32%)	NS
Delayed gastric emptying	3 (16%)	1 (4%)	NS
Abdominal infection	5 (26%)	10 (40%)	NS
Seroperitoneum	5 (26%)	10 (40%)	NS
Pneumonia	2 (11%)	7 (28%)	NS
Reoperation	2 (11%)	3 (12%)	NS
Pancreatic duct diameter >3 mm	n = 23	n = 25	
Postoperative pancreatic fistula	10 (43%)	9 (36%)	NS
Grade A	9 (39%)	5 (20%)	NS
Grade B	1 (4%)	2 (8%)	NS
Grade C	0	2 (8%)	NS
Grade B + C	1 (4%)	4 (16%)	NS
Delayed gastric emptying	4 (17%)	4 (16%)	NS
Abdominal infection	2 (9%)	4 (16%)	NS
Seroperitoneum	5 (22%)	5 (20%)	NS
Pneumonia	3 (13%)	4 (16%)	NS
Reoperation	2 (9%)	2 (8%)	NS

NS = not significantly different.

Table 7

Pancreatic fistula and pancreatic texture.

	Ulinastatin group	Placebo group	*P*
Soft texture	n = 20	n = 24	
Postoperative pancreatic fistula	9 (45%)	17 (71%)	0.083
Grade A	7 (35%)	10 (42%)	NS
Grade B	0	5 (21%)	0.053
Grade C	2 (10%)	2 (8%)	NS
Grade B + C	2 (10%)	7 (29%)	NS
Delayed gastric emptying	5 (25%)	2 (8%)	NS
Abdominal infection	5 (25%)	9 (38%)	NS
Seroperitoneum	6 (30%)	9 (38%)	NS
Pneumonia	2 (10%)	6 (25%)	NS
Reoperation	2 (10%)	3 (13%)	NS
Hard texture	n = 22	n = 26	
Postoperative pancreatic fistula	9 (41%)	11 (42%)	NS
Grade A	8 (36%)	6 (23%)	NS
Grade B	1 (5%)	3 (12%)	NS
Grade C	0	2 (8%)	
Grade B + C	1 (5%)	5 (19%)	NS
Delayed gastric emptying	2 (9%)	3 (12%)	NS
Abdominal infection	2 (9%)	5 (19%)	NS
Seroperitoneum	4 (18%)	6 (23%)	NS
Pneumonia	3 (14%)	5 (19%)	NS
Reoperation	2 (10%)	2 (8%)	NS

NS = not significantly different.

POPF, the amylase concentration could be much lower when placing the drainage tube apart from the pancreatic anastomotic stoma instead of placing it near the anastomotic stoma like we did in this study. Moreover, Kurumboor et al[23] reported a prospective randomized trial, with a high POPF rate of 63% in control group and 60% in octreotide treatment group. Severe POPF rate in their control group was a little lower than that in our placebo group (18.5% vs 24.0%); however, the rate in their octreotide treatment group was higher than that in our ulistatin group (10.9% vs 7.1%). It might indicate that ulinastatin had a more preventive effect on POPF than octreotide.

Octreotide is a synthetic octapeptide analog of native somatostatin, which has been shown to rapidly decrease output from, and facilitate closure of, pancreatic fistulas.[24,25] However, more reports suggested that octreotide is not beneficial for POPF after pancreatic surgery.[18,23,26,27] Lowy et al[26] evaluated 110 patients undergoing PD and found that the rates of clinical pancreatic fistula and perioperative complications were 6% and 25% in the control group, and 12% and 30% in the octreotide group.

POPF may be related to the higher incidence of hemorrhage, abdominal infection, seroperitoneum, and pneumonia in patients who underwent PD ($P = 0.051$, $P = 0.006$, $P = 0.010$, and $P = 0.001$, respectively). More frequent reoperations and longer postoperative hospital stays were needed by patients with POPF ($P = 0.074$ and $P = 0.002$, respectively).

In our study, ulinastatin could significantly reduce the occurrence of POPF of grade B and grade B + C; however, it did not influence on other prognosis. The mechanism of the occurrence of POPF after PD was still unclear. It seemed to be relative to the leakage of pancreatic juice in pancreatic duct.[28,29] For grade A PF, it usually did not lead to serious consequences and would be self-healing after proper drainage, as the pancreatic juice filtering into abdominal cavity did not contact with the digestive juice and was not activated. If the pancreatic juice was activated by the digestive juice, PF of grade B or C would happen with severe complications, such as infection and bleeding, and even death.[30]

Ulinastatin could prevent and treat acute pancreatitis with the inhibition of pancreatic enzyme activation, and control the inflammatory reactions with the suppression of many enzymes, such as trypsin, α-chymotrypsin, lipoprotein lipase, and hyaluronidase, and a variety of inflammatory mediators, such as interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor-α.[31] Ulinastatin could reduce POPF of grade B and grade B + C because it could prevent the development from the mild POPF of grade A to severe POPF through a similar way.

Nonsurgical risk factors for PF after PD mainly included patients older than 65 years, preoperative hyperbilirubinemia, small diameter of the pancreatic duct, soft pancreas, and so on.[32] Small diameter of the pancreatic duct and soft pancreas were considered the most important factors.[33]

It had been reported that the incidence of POPF was significantly higher in patients with pancreatic duct size ≤3 mm than >3 mm (25% vs 8%, $P = 0.037$).[34] Additionally, narrowing of the pancreatic duct increased the odds of suffering a clinically relevant PF by 68% for each 1-mm decrease in diameter.[35] Akamatsu et al[36] suggested that the diameter of the main pancreatic duct could be a reliable predictor of POPF after PD. In this study, the incidence of POPF was also significantly associated with the pancreatic duct diameter (≤3 mm, 61.4% vs >3 mm, 39.6%; $P = 0.037$). For patients with small pancreatic duct diameter (≤3 mm), using ulinastatin was a significant protective factor of POPF and grade B POPF after PD ($P = 0.083$, $P = 0.053$).

POPF was strongly predicted by pancreatic texture.[37] In Tajima et al's study,[34] POPF showed an incidence of 3% in hard, 20% in intermediate, and 23% in soft pancreatic texture ($P = 0.046$). Hard pancreas could bear higher tension of suture than soft pancreas, and had decreased exocrine function to reduce the risk of POPF.[29] In our study, there were more POPFs happening to patients with soft pancreas, but not statistically significant ($P = 0.095$). Ulinastatin had some protective effects on POPF and grade B POPF for patients with soft texture ($P = 0.083$, $P = 0.053$).

In conclusion, ulinastatin could significantly reduce severe POPF for patients who underwent PD. It also had significant protective effects on POPF for patients with small pancreatic duct diameter (≤3 mm). Using ulinastatin was an effective strategy for preventing severe POPF after PD.

Acknowledgements

The authors thank Dr. Xin Zhang in the Department of Epidemiology, West China Hospital, Sichuan University for supporting and helping us. Thanks to the doctors and nurses in the Department of Pancreatic Surgery, operating room and Intensive Care Unit, West China Hospital, Sichuan University.

References

[1] Pedrazzoli S, DiCarlo V, Dionigi R, et al. Standard versus extended lymphadenectomy associated with pancreatoduodenectomy in the surgical treatment of adenocarcinoma of the head of the pancreas: a multicenter, prospective, randomized study. Lymphadenectomy Study Group. Ann Surg 1998;228:508–17.

[2] Yeo CJ, Cameron JL, Sohn TA, et al. Pancreaticoduodenectomy with or without extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma: comparison of morbidity and mortality and short-term outcome. Ann Surg 1999;229:613–22.

[3] Conlon KC, Klimstra DS, Brennan MF. Long-term survival after curative resection for pancreatic ductal adenocarcinoma. Clinicopathologic analysis of 5-year survivors. Ann Surg 1996;223:273–9.
[4] Phan GQ, Yeo CJ, Cameron JL, et al. Pancreaticoduodenectomy for selected periampullary neuroendocrine tumors: fifty patients. Surgery 1997;122:989–6.
[5] Barens SA, Lillemoe KD, Kaufman HS, et al. Pancreaticoduodenectomy for benign disease. Am J Surg 1996;171:131–4.
[6] Burcharth F, Olsen SD, Trillingsgaard J, et al. Pancreaticoduodenectomy for periampullary cancer in patients more than 70 years of age. Hepatogastroenterology 2001;48:1149–52.
[7] Lieberman MD, Kilburn H, Lindsey M, et al. Relation of perioperative deaths to hospital volume among patients undergoing pancreatic resection for malignancy. Ann Surg 1995;222:638–45.
[8] Buchler MW, Wagner M, Schmied BM, et al. Changes in morbidity after pancreatic resection: toward the end of completion pancreatectomy. Arch Surg 2003;138:1310–4.
[9] Bassi C, Falconi M, Salvia R, et al. Management of complications after pancreaticoduodenectomy in a high volume centre: results on 150 consecutive patients. Digest Surg 2001;18:453–7.
[10] Gouma DJ, van Geenen RC, van Gulik TM, et al. Rates of complications and death after pancreaticoduodenectomy: risk factors and the impact of hospital volume. Ann Surg 2000;232:786–95.
[11] Lermite E, Sommacale D, Piardi T, et al. Complications after pancreatic resection: diagnosis, prevention and management. Clin Res Hepatol Gastroenterol 2013;37:230–9.
[12] Butturini G, Daskalaki D, Molinari E, et al. Pancreatic fistula: definition and current problems. J Hepatobiliary Pancreat Surg 2008;15:247–51.
[13] Ho CK, Kleeff J, Friess H, et al. Complications of pancreatic surgery. HPB 2005;7:99–108.
[14] DeOliveira ML, Winter JM, Schafer M, et al. Assessment of complications after pancreatic surgery: A novel grading system applied to 633 patients undergoing pancreaticoduodenectomy. Ann Surg 2006;244:931–7.
[15] Bassi C, Dervenis C, Butturini G, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005;138:8–13.
[16] Satoi S, Toyokawa H, Yanagimoto H, et al. Is a nonstented duct-to-mucosa anastomosis using the modified Kakita method a safe procedure? Pancreas 2010;39:165–70.
[17] Sutton CD, Garcea G, White SA, et al. Isolated Roux-loop pancreaticojejunostomy: a series of 61 patients with zero postoperative pancreaticoenteric leaks. J Gastrointest Surg 2004;8:701–5.
[18] Yeo CJ, Cameron JL, Lillemoe KD, et al. Does prophylactic octreotide decrease the rates of pancreatic fistula and other complications after pancreaticoduodenectomy? Results of a prospective randomized placebo-controlled trial. Ann Surg 2000;232:419–29.
[19] Ohnishi H, Kosuzume H, Ashida Y, et al. Effects of urinary trypsin inhibitor on pancreatic enzymes and experimental acute pancreatitis. Dig Dis Sci 1984;29:26–32.
[20] Oda T, Miyawaki T, Sameshima T, et al. Antishock effects of urinary trypsin inhibitor, MR-20. Masui. Jpn J Anesthesiol 1984;33:137–42.
[21] Okuhama Y, Shiraishi M, Higa T, et al. Protective effects of ulinastatin against ischemia-reperfusion injury. J Surg Res 1999;82:34–2.
[22] Xiong JJ, Altaf K, Mukherjee R, et al. Systematic review and meta-analysis of outcomes after intraoperative pancreatic duct stent placement during pancreaticoduodenectomy. Br J Surg 2012;99:1050–61.
[23] Kurumboor P, Palaniswami KN, Pramil K, et al. Octreotide does not prevent pancreatic fistula following pancreatoduodenectomy in patients with soft pancreas and non-dilated duct: a prospective randomized controlled trial. J Gastrointest Surg 2015;19:2038–44.
[24] Pederzoli P, Bassi C, Falconi M, et al. Conservative treatment of external pancreatic fistulas with parenteral nutrition alone or in combination with continuous intravenous infusion of somatostatin, glucagon or calcitonin. Surg Gynecol Obstet 1986;163:428–32.
[25] Prinz RA, Pickleman J, Hoffman JP. Treatment of pancreatic cutaneous fistulas with a somatostatin analog. Am J Surg 1988;155:36–42.
[26] Lowy AM, Lee JE, Pisters PW, et al. Prospective, randomized trial of octreotide to prevent pancreatic fistula after pancreaticoduodenectomy for malignant disease. Ann Surg 1997;226:632–41.
[27] Droeser RA, Jeanmonod P, Schuld J, et al. Octreotide prophylaxis is not beneficial for biochemical activity and clinical severity of postoperative pancreatic fistula after pancreatic surgery. Dig Surg 2012;29:484–91.
[28] Noda H, Kamiyama H, Kato T, et al. Risk factor for pancreatic fistula after pancreaticoduodenectomy performed by a surgeon during a learning curve: analysis of a single surgeon's experiences of 100 consecutive patients. Hepatogastroenterology 2012;59:1990–3.
[29] Ramacciato G, Mercantini P, Petrucciani N, et al. Risk factors of pancreatic fistula after pancreaticoduodenectomy: a collective review. Am Surg 2011;77:257–69.
[30] Lermite E, Pessaux P, Brehant O, et al. Risk factors of pancreatic fistula and delayed gastric emptying after pancreaticoduodenectomy with pancreaticogastrostomy. J Am Coll Surg 2007;204:588–96.
[31] Chen CC, Wang SS, Lee FY. Action of antiproteases on the inflammatory response in acute pancreatitis. JOP 2007;8(4 suppl):488–94.
[32] Berberat PO, Friess H, Kleeff J, et al. Prevention and treatment of complications in pancreatic cancer surgery. Dig Surg 1999;16:327–6.
[33] Yang YM, Tian XD, Zhuang Y, et al. Risk factors of pancreatic leakage after pancreaticoduodenectomy. World J Gastroenterol 2005;11:2456–1.
[34] Tajima Y, Kuroki T, Tsutsumi R, et al. Risk factors for pancreatic anastomotic leakage: the significance of preoperative dynamic magnetic resonance imaging of the pancreas as a predictor of leakage. J Am Coll Surg 2006;202:723–1.
[35] Pratt WB, Callery MP, Vollmer CMJr. Risk prediction for development of pancreatic fistula using the ISGPF classification scheme. World J Surg 2008;32:419–28.
[36] Akamatsu N, Sugawara Y, Komagome M, et al. Risk factors for postoperative pancreatic fistula after pancreaticoduodenectomy: the significance of the ratio of the main pancreatic duct to the pancreas body as a predictor of leakage. J Hepatobiliary Pancreat Sci 2010;17:322–8.
[37] Lin JW, Cameron JL, Yeo CJ, et al. Risk factors and outcomes in postpancreaticoduodenectomy pancreaticocutaneous fistula. J Gastrointest Surg 2004;8:951.