Preventive effects of ulinastatin on complications related to pancreaticoduodenectomy
A Consort-prospective, randomized, double-blind, placebo-controlled trial

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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 (<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: SGPFF = International Study Group of Pancreatic Fistula, PD = Pancreaticoduodenectomy, POPF = Postoperative pancreatic fistula, SD = Standard deviation.

Keywords: pancreaticoduodenectomy, postoperative pancreatic fistula, ulinastatin

1. Introduction
Pancreatoduodenectomy (PD) is an effective strategy for various malignant and benign diseases of pancreas and periampullary region. Along with technical advances, PD has become a surgical procedure with a <5% perioperative death rate. 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.

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

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. Clinically, ulinastatin is mainly used to treat acute pancreatitis, chronic recurrent pancreatitis, and acute circulatory failure. 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
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 pancreato-toduodenectomy 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 pancreateoduodenectomy was conducted for each patient in this study. Standard or enlarge lymphadenectomy was chosen according to patient’s condition. Some patients underwent pancreateoduodenectomy 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 300,000U of ulinastatin (Guangdong Techpool Bio-pharma Co, Ltd., Guangdong, China) dissolved in 100mL of 0.9% saline solution and administered by intravenous drip infusion starting just before the surgery for 120 minutes. Then 600,000U of ulinastatin with 50mL 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, Na₂HPO₄, and NaH₂PO₄, 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 x² 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,
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 adenosquamous carcinoma, 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, sepsisemia, and multiple organ dysfunction syndrome.

### Table 1
Baseline characteristics and preoperative factors of patients in the trial group and the control group.

|                          | Ulinastatin group | Placebo group | $P$  |
|--------------------------|-------------------|---------------|------|
| Age, y, mean±SD          | 56.83±12.20       | 56.76±11.99   | NS   |
| Sex (female)             | 18 (43%)          | 14 (28%)      | NS   |
| BMI, kg/m², 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%)      | 4 (9%)        | 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   |
| Hyperproteinemia         | 5 (12%)           | 8 (16%)       | NS   |
| Gastric intraluminal bleeding | 0            | 1 (2%)        | NS   |
| Weight loss              |                   |               |      |
| <5                       | 39 (93%)          | 41 (82%)      | NS   |
| >5                       | 3 (7%)            | 9 (18%)       | NS   |
| Jaundice                 |                   |               |      |
| No                       | 16 (38%)          | 25 (50%)      | NS   |
| Mild and moderate        | 15 (36%)          | 10 (20%)      | NS   |
| Severe                   | 11 (26%)          | 15 (30%)      | NS   |
| 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 | Placebo group | $P$  |
|--------------------------|-------------------|---------------|------|
| Operative method         |                   |               |      |
| Laparotomy               | 39 (93%)          | 47 (94%)      | NS   |
| Endoscope                | 3 (7%)            | 3 (6%)        | NS   |
| Type of resection        |                   |               |      |
| Standard                 | 39 (93%)          | 46 (92%)      | NS   |
| Pylorus-preserving        | 3 (7%)            | 4 (8%)        | NS   |
| Vein resection           | 5 (12%)           | 5 (10%)       | NS   |
| Lymphadenectomy          |                   |               |      |
| Standard                 | 31 (74%)          | 37 (74%)      | NS   |
| Enlarge                  | 3 (7%)            | 4 (8%)        | NS   |
| Transfusion              | 6 (14%)           | 6 (12%)       | NS   |
| Pancreas texture         |                   |               |      |
| Soft                     | 20 (48%)          | 24 (48%)      | NS   |
| Hard                     | 22 (52%)          | 26 (52%)      | NS   |
| Pancreatic duct diameter, mm |                   |               |      |
| ≤3                      | 19 (45%)          | 25 (50%)      | NS   |
| >3                      | 23 (55%)          | 25 (50%)      | NS   |
| Bile duct diameter, cm   |                   |               |      |
| <1                      | 10 (24%)          | 19 (38%)      | NS   |
| ≥1                      | 32 (76%)          | 31 (62%)      | NS   |
| Drainage of the pancreatic duct |             |               |      |
| Internal                 | 20 (48%)          | 21 (42%)      | NS   |
| External                 | 22 (52%)          | 29 (58%)      | NS   |
| Operation time, h        |                   |               |      |
| <6                      | 29 (69%)          | 28 (56%)      | NS   |
| ≥6                      | 13 (31%)          | 22 (44%)      | NS   |

NS = not significantly different.

### Table 3
Pathologic findings of patients in the trial group and the control group.

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

NS = not significantly different.

*Includes solid pseudopapillary neoplasm, intraductal papillary-mucinous neoplasm of the pancreas, periampullary adenocarcinoma, periampullarystromal tumor, autoimmune pancreatitis, and duodenal stromal tumor.
3.4. Risk factors of POPF

In univariate regression analysis, treatment with ulinastatin had no association with the occurrence of POPF \( (P=0.211; \text{odds ratio [OR]: 0.589, 95\% confidence interval [CI]: 0.258–1.348}) \), but was related to severe pancreatic fistula \( (\text{OR: 0.246, 95\% CI: 0.064–0.932}) \), 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 \( \leq 3\) mm, which was significantly higher than that in patients without fistula \( (37\%; \ P=0.037; \text{Table 5}) \). Ulinastatin could significantly reduce the presence of POPF and grade B POPF in patients with a pancreatic duct diameter \( \leq 3\) mm \( (P=0.022 \text{ and } P=0.029, \text{respectively; Table 6}) \).

In patients with PF, 57\% had soft pancreas, which was comparable with that in patients without fistula \( (39\%; \ P=0.095; \text{Table 5}) \). Ulinastatin also had some protective effect on POPF and grade B POPF for patients with soft pancreas \( (P=0.083 \text{ and } P=0.053, \text{respectively; Table 6}) \).

After adjustment for pancreatic duct diameter and pancreas texture, ulinastatin group had a decreased risk of severe pancreatic fistula \( (\text{grade B+C, } P=0.043; \text{OR: 0.246, 95\% CI: 0.064–0.935}) \).

4. Discussion

In the current study, the overall incidence of postoperative complications was 71\% \( (659/92) \). 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
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 ulinastatin group (10.9% vs 7.1%). It might indicate that ulinastatin had a more preventive effect on POPF than octreotide.

Ocrotectin 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[24] 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, seropertitoneum, 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.

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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  |
| Seropertitoneum                         | 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                                 | 0                | 3 (12%)       | NS  |
| Grade C                                 | 0                | 2 (8%)        | NS  |
| Grade B+C                               | 1 (5%)           | 5 (19%)       | NS  |
| Delayed gastric emptying                | 2 (9%)           | 3 (12%)       | NS  |
| Abdominal infection                     | 2 (9%)           | 5 (19%)       | NS  |
| Seropertitoneum                         | 4 (18%)          | 6 (23%)       | NS  |
| Pneumonia                               | 3 (14%)          | 5 (19%)       | NS  |
| Reoperation                             | 2 (10%)          | 2 (8%)        | NS  |

NS =not significantly different.
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