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Effects of Fasting and Administration of Octreotide Acetate and Ulinastatin on Clinical Outcomes of Pancreatic Fistula After Pancreatoduodenectomy

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Objective: Postoperative pancreatic fistula (POPF) following pancreaticoduodenectomy is the most serious complication of these surgical procedures; therefore, we examined the effectiveness of fasting, and administration of octreotide acetate and ulinastatin as a method of prevention.

Summary of Background Data: Although various drug therapies and surgical techniques have been used for the treatment of POPF, no decisive treatment for POPF exists.

Methods: The clinical course of 30 patients who developed POPF was retrospectively evaluated and compared among no dietary intake (n = 18), octreotide acetate (n = 8), and ulinastatin (n = 8) using an overlapping design. Patients were allocated to either the dietary intake or fasting (no dietary intake) group, and those in the no dietary intake group were further divided into the octreotide acetate or ulinastatin group.

Results: Length of hospitalization was longer for the no dietary intake group than for the dietary intake group ($P = 0.002$). When considering only grade B or C POPF cases, the no dietary intake group had a longer length of hospitalization and a higher white blood cell count on day 7 after the diagnosis of POPF than the dietary intake group ($P < 0.05$). The white blood cell count was also higher in the octreotide acetate group than in the ulinastatin group ($P = 0.021$). The length of hospitalization was shorter in the ulinastatin group than in the octreotide acetate group ($P = 0.025$).

Conclusions: The use of no dietary intake, octreotide acetate, and ulinastatin does not seem to contribute to the clinical course of patients with POPF after pancreatoduodenectomy.

Key words: Pancreatoduodenectomy – Fasting – Octreotide – Ulinastatin

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Pancreatoduodenectomy (PD) is a surgical procedure used as treatment for both benign and malignant diseases of the pancreatic head region, and it is one of the most technically demanding gastrointestinal surgeries to perform.[1] Postoperative pancreatic fistula (POPF) is the most critical complication of PD, with a relatively high incidence rate of 2% to 28%,[1–4] and carries the risk of intraperitoneal bleeding and postoperative mortality.[5] In the presence of POPF, trypsinogen, a protein fusion enzyme existing as an inactive substance in pancreatic fluid, transforms into trypsin, its active form, in the presence of intestinal fluids or bile, including activated enterokinase. The activated trypsin in turn activates other protein fusion enzymes, inducing damage to adjacent tissues via autophagia. As a result, intraperitoneal bleeding due to ruptured pseudoaneurysm, multiorgan failure due to intraperitoneal abscess, or sepsis induced by infectious pancreatic fluid may occur. The incidence of intraperitoneal bleeding after PD ranges between 1% and 8% worldwide,[5–11] with the associated mortality rate of as high as 11% to 58%.[7–15]

Although various drug therapies and surgical techniques have been used for the treatment of POPF, a decisive treatment for POPF has not yet been defined. Fasting is one of the possible medical interventions for the treatment of POPF. The rationale for fasting as an intervention is that oral intake induces the secretion of secretin or cholecystokinin, which promotes pancreatic exocrine function, leading to an exacerbation of POPF.[16] Fujii *et al*[17] evaluated the effects of fasting by randomizing 59 patients who developed POPF 5 days after PD to an oral intake group (n = 30) and fasting group (n = 29), and they compared the following factors between the 2 groups: duration of drain placement, grade of pancreatic fistula, presence or absence of intraperitoneal bleeding, length of hospitalization, and mortality rate during hospitalization. Fujii *et al*[17] concluded that oral intake did not prolong the period of drain placement nor did it exacerbate the pancreatic fistula. Drug therapies, as well as the use of fibrin glue applied to the pancreatic-digestive anastomotic region, and intra- and postoperative administration of octreotide acetate (OC) and ulinastatin (UTI), also have been used as treatment options for POPF, but with limited reported evidence of success.[18–26] Therefore, the purpose of this study was to confirm the effects of fasting (no dietary intake [NDI]) and the administration of OC and UTI for the treatment of POPF.

Materials and Methods

Study design and population

We conducted a retrospective comparative study to evaluate the clinical outcomes of NDI, OC, and UTI treatment in patients with POPF after PD in Jikei University Hospital between January 2009 and December 2013. Our study was approved by Jikei University School of Medicine (review number: 26-070[7575]). As this was a database survey, informed consent was not requested. Inclusion criterion was patients who underwent PD as an operative indication for periampullary cancer. The surgical method for PD, as well as intraoperative and postoperative management, was conducted according to the usual procedures in our hospital. PD or subtotal stomach-preserving pancreatoduodenectomy with D2 dissection was performed based on the extent of the tumor or the preference of the attending surgeon. Reconstruction was conducted using the modified Child method. Basically, pancreaticojejunostomy was performed in 2 layers, using an end-to-side and duct-to-mucosa approach, with an external transabdominal pancreatic duct stent. After reconstruction, one drain was placed at the pancreaticojejunostomy and hepaticojejunostomy through the foramen of Winslow, and another near the pancreaticojejunostomy. All patients received prophylactic antibiotics (cefmetazole Na 2 g/d) for 3 days postoperatively.

Of the 90 patients included in the study, POPF developed in 30 (33.3%). The diagnosis of POPF was based on the diagnostic criteria of the International Study Group on Pancreatic Fistula.[2] Although oral dietary intake began on postoperative day 4 in all patients who did not develop a POPF, those who did develop a POPF were allocated to either the oral dietary intake (DI, 12 patients) or fasting group (NDI, 18 patients), at the discretion of the treating physician. Patients in the NDI group were further allocated to the OC (300–600 μg/d, 24 h continuous) or UTI group (100,000–150,000 U/d, divided in 2 or 3 equal daily doses), also at the discretion of the treating physician.

Clinical outcomes were evaluated based on blood samples drawn every other day and computed tomography imaging performed as required. Therapy was continued until resolution of fever, cessation of abdominal pain, elevation of blood inflammatory markers, and elevation of amylase in the drained fluid. Discharge criteria included healing of the pancreatic fistula, absence of subjective symptoms, adequate oral DI, and return to basic

Table 1 Patient characteristics (n = 30)

Factor	NDI group (n = 18)	DI group (n = 12)	*P* value
Age, y[a]	68.2	66.8	0.703
Sex, male:female	15:3	8:4	0.392
Disease			0.621
Pancreatic cancer	6	4	
Bile duct cancer	5	5	
IPMN	5	3	
Other	2	0	
Diagnostic criteria			0.063
Drain	14	5	
CT	4	7	
The day of diagnosis of POPF (POD)[a]	8.2	9.4	0.157

CT, computed tomography; DI, dietary intake; IPMN, intraductal papillary mucinous neoplasm; NDI, no dietary intake; POPF, postoperative pancreatic fistula; POD, postoperative day.

[a]Values are expressed as mean.

activities of daily living. After discharge, all patients were followed-up through the outpatient clinic.

Measured variables

The following variables were measured for analysis: amylase level in the serum and drain discharge; length of hospitalization; duration of antibacterial drug administration; period of leukocytosis; white blood cell count (WBC) on day 7 after POPF diagnosis; POPF grade; and presence or absence of drain reinsertion, drain replacement, and intraperitoneal bleeding.

Statistical analysis

Data are expressed as a mean ± SD. Measured variables were compared between the groups using a *t* test or χ^2 test as appropriate for the data type and distribution. A *P* value of <0.05 was considered significant. All analyses were performed using SPSS (version 20.0; IBM Japan, Tokyo, Japan).

Results

Relevant background characteristics of the 30 patients who developed POPF are summarized in Table 1. There was no significant difference between NDI and DI groups regarding age, sex, disease, diagnostic criteria of pancreatic fistula, and period from the surgery to the time of POPF diagnosis. The length of hospitalization was significantly longer in the NDI group than in the DI group ($P = 0.002$), with a higher incidence of intraperitoneal bleeding in the NDI group than in the DI group ($P = 0.024$, Table 2). Among the 30 patients who developed a POPF, a POPF grade B or C was identified in 26 patients (17 in the NDI group and 9 in the DI group). On subgroup analysis of such patients, length of hospitalization was again longer in the NDI group than in the DI group ($P = 0.003$), with a higher WBC at 7 days after diagnosis in the NDI group than in the DI group ($P = 0.028$, Table 3).

Regarding OC, 8 patients were in the NDI group and the other 22 in the DI group. The WBC was significantly higher at 7 days after the diagnosis of POPF in the OC group than in the non-OC group (22 patients; $P = 0.021$; Table 4). The effects of UTI administration are shown in Table 5. The length of hospitalization was significantly longer in the UTI than in the non-UTI group ($P = 0.025$).

Overall, NDI, OC, and UTI did not result in any significant favorable clinical outcome compared with DI.

Table 2 Results of NDI (n = 30)

Factor	NDI group (n = 18)	DI group (n = 12)	*P* value
Amylase of drain discharge, IU/L[a]	46,015.50	27,165.60	0.42
Postoperative length of stay, d[a]	47.1	29.2	0.003
Length of stay after diagnosis of POPF, d[a]	38.9	19.8	0.002
Length of antibiotics administered, d[a]	17.5	10.3	0.077
Length of leukocytosis, d[a]	11.5	5.6	0.055
WBC value on day 7, /μL[a]	8833.3	8260	0.722
Grade of POPF (criteria of ISGPF) A:B:C	1:13:4	3:8:1	0.234
Drain replaced, n (%)	11 (61)	5 (42)	0.457
Drain exchanged, n (%)	8 (44)	2 (17)	0.235
Intra-abdominal hemorrhage, n (%)	7 (39)	0 (0)	0.024

DI, dietary intake; ISGPF, International Study Group of Postoperative Pancreatic Fistula; NDI, no dietary intake; POPF, postoperative pancreatic fistula; WBC, white blood cell.

[a]Values are expressed as mean.

Table 3 Results of NDI (POPF grade B or C only) (n = 26)

Factor	NDI group (n = 17)	DI group (n = 9)	*P* value
Amylase of drain discharge, IU/L[a]	47,826	27,165.60	0.392
Postoperative length of stay, d[a]	47.9	31.1	0.007
Length of stay after diagnosis of POPF, d[a]	39.7	21	0.003
Length of antibiotics administered, d[a]	17.9	11.9	0.203
Length of leukocytosis, d[a]	12.1	4.9	0.01
WBC value on day 7, /μL[a]	8958.8	7485.7	0.438
Drain replaced, n (%)	11 (65)	5 (56)	0.692
Drain exchanged, n (%)	8 (47)	2 (22)	0.399
Intra-abdominal hemorrhage, n (%)	7 (41)	0 (0)	0.058

DI, dietary intake; NDI, no dietary intake; POPF, postoperative pancreatic fistula; WBC, white blood cell.

[a]Values are expressed as mean.

Discussion

POPF is a critical complication of PD that increases the medical intervention required, prolongs hospitalization, increases the risk for morbidity and mortality, and decreases patient-reported quality of life. It is common for patients with a POPF to be on a prolonged period of fasting, requiring intravenous hyperalimentation for nutritional management, as well as the use of drug therapy to suppress the production of pancreatic fluid. Treatment of the POPF itself and treatments targeting biochemical and drug-specific effects have been evaluated. In the current study, we focused on evaluating the effects of NDI, OC, and UTI, and demonstrated no positive effect of any of them for POPF.

The effect of OC on the pancreatic fistula has been evaluated in numerous randomized studies, with no evidence of a positive effect identified.[20–24,27] However, 2 studies have reported a reduced incidence of POPF among patients treated with OC,[28,29] including a significantly shorter time to closure of the POPF.[30] Therefore, it has been suggested that OC may reduce the risk of POPF, with a possible advantage of prophylactic administration of OC.[31,32] Contrary to these findings, the current study demonstrated that OC administration was associated with a significantly higher WBC at 7 days after POPF diagnosis, with no favorable effect of OC on the measured outcomes noted.

UTI has been used clinically to alleviate acute circulatory disorders induced by acute or chronic pancreatitis, with evidence of effectiveness for the prevention of pancreatitis after endoscopic retrograde cholangiopancreatography.[33] However, 2 recent studies indicated that the incidence of postoperative pancreatitis was higher than expected after PD, with an associated increased risk for POPF.[34,35] To address this issue, Zhang *et al*[36] administered UTI intraoperatively and postoperatively in patients who underwent PD, and reported a decrease in the incidence rate of POPF (grade B or higher) compared with the placebo group. Uemura *et al*[37] reported that the group with UTI administered during the perioperative period was associated with a significant decrease in the level of amylase

Table 4 Results of octreotide (n = 30)

Factor	OC group (n = 8)	Non-OC group (n = 22)	*P* value
Amylase of drain discharge, IU/L[a]	54,546.30	33,185.10	0.314
Postoperative length of stay, d[a]	49.8	36.3	0.089
Length of stay after diagnosis of POPF, d[a]	41.6	27.5	0.07
Length of antibiotics administered, d[a]	17.4	13.6	0.415
Length of leukocytosis, d[a]	12.6	7.9	0.224
WBC value on day 7, /μL[a]	11,300	7560	0.021
Grade of POPF (criteria of ISGPF) A:B:C	0:7:1	4:14:4	0.36
Drain replaced, n (%)	6 (75)	10 (45)	0.226
Drain exchanged, n (%)	2 (25)	8 (36)	0.682
Intra-abdominal hemorrhage, n (%)	3 (37)	4 (18)	0.589

ISGPF, International Study Group of Postoperative Pancreatic Fistula; OC, octreotide; POPF, postoperative pancreatic fistula; WBC, white blood cell.

[a]Values are expressed as mean.

Table 5 Results of ulinastatin (n = 30)

Factor	UTI group (n = 8)	Non-UTI group (n = 22)	*P* value
Amylase of drain discharge, IU/L[a]	49,782.10	35,964.20	0.518
Postoperative length of stay, d	51.9	35.6	0.036
Length of stay after diagnosis of POPF, d[a]	43.9	26.6	0.025
Length of antibiotics administered, d[a]	15.9	14.1	0.71
Length of leukocytosis, d[a]	9.3	9.1	0.968
WBC value on day 7, /μL[a]	7725	8990	0.457
Grade of POPF (criteria of ISGPF) A:B:C	1:7:0	3:14:5	0.316
Drain replaced, n (%)	4 (50)	12 (55)	0.825
Drain exchanged, n (%)	3 (37)	7 (32)	0.77
Intra-abdominal hemorrhage, n (%)	2 (25)	5 (23)	0.896

ISGPF, International Study Group of Postoperative Pancreatic Fistula; POPF, postoperative pancreatic fistula; UTI, ulinastatin; WBC, white blood cell.

[a]Values are expressed as mean.

on postoperative days 1 and 3 compared with the placebo group; however, this prophylactic effect of UTI was not supported by a recent study evaluating the incidence rate of pancreatitis associated with endoscopic procedures.[38] In the current study, UTI administration was associated with a significantly longer length of hospitalization, with no indication of a favorable effect of UTI on clinical outcomes. It is important to note, however, that there are only a few reports currently available regarding the effects of UTI administration on POPF incidence. Therefore, the effects of UTI administration currently remain controversial.

DI induces the secretion of secretin and cholecystokinin, as well as promotes pancreatic exocrine function, which leads to exacerbation of the POPF. As previously described, Fujii *et al*[17] did not identify a therapeutic benefit of fasting (NDI) over DI, concluding that fasting may not be required after PD surgery to reduce the risk of POPF. Klek *et al*,[39] however, did provide evidence in their randomized trial that nasogastric tube feeding of patients with POPF after PD (where PD included distal pancreatectomy, necrosectomy, and gastrectomy) significantly shortened the length of hospitalization compared with intravenous hyperalimentation by achieving pancreatic fistula resolution. This finding, however, should be cautiously considered for practice considering the findings of a similar study that reported an exacerbation of pancreatic juice leakage with nasogastric feeding under similar conditions.[40–43] Moreover, a multi-institutional, randomized controlled trial, which included 204 patients after PD, comparing the clinical course of patients provided with nasojejunal early enteral nutrition with those receiving total parenteral nutrition, reported that nasojejunal early enteral nutrition was associated with a higher rate of POPF (48.1% versus 27.7%, respectively; $P = 0.012$) and grade B or C of POPF (29.4% versus 13.9%, respectively; $P = 0.007$).[44] In the present study, the length of hospitalization was longer in the NDI group than in the DI group, with a higher incidence of intraperitoneal bleeding in the NDI group. According to a subanalysis of patients with grade B or C POPF, NDI was associated with a longer length of hospitalization and higher WBC; therefore, we did not identify any clinical advantage of NDI among patients who developed POPF after PD.

The primary rationale for fasting after PD was to lower the risk of POPF. Specifically, it has been postulated that oral intake may be associated with a lower secretion of secretin and cholecystokinin in the duodenum and upper jejunum in patients who have undergone PD than in healthy individuals. However, although some studies have confirmed a decrease in secretin and cholecystokinin after PD, others did not find a statistically significant difference.[45–48] Therefore, there remains no strong evidence to support the use of NDI after PD. However, there is general agreement that enteral nutrition has a more favorable impact on recovery than parenteral nutrition, promoting better wound healing and decreasing exuberant granulation tissue.[49] Moreover, related studies have suggested that DI may improve a patient's nutritional condition, as well as increase intestinal immunity. DI further promotes and improves self-reported satisfaction with daily life and quality of life.[50]

Based on the evidence available, suppression of the production of digestive fluids may not improve the clinical course of POPF after PD. Moreover, fasting may indeed have a negative impact on intestinal immunity and nutritional status. In

addition, long-term fasting may induce a decline in the function of the intestinal mucosa and pancreatic excretion, resulting in metabolic complications, such as morphological degeneration in the intestinal mucosa.[51]

Evaluation of clinical outcomes of interventions for POPF is important because unnecessary medical intervention can increase health care costs. Moreover, fasting, OC, and UTI typically require placement of a central venous catheter, which increases the risk for infection, as well as complications at the site of insertion.

The most prominent limitation of the current study was the fact that allocation of patients to the NDI, OC, and UTI groups was based on the subjective preference of the attending physician rather than by randomization. Thus, the groups were not balanced for comparison, which may have introduced significant bias and affected our results. Furthermore, the sample size was small, and all the patients were from one hospital. Thus, for future investigation, a multicenter randomized controlled study involving a larger number of patients is warranted to provide stronger evidence supporting the findings of the present study.

Conclusions

In conclusion, our data indicate that NDI, OC, and UTI did not confer a therapeutic benefit to the clinical course of patients with POPF after PD. Therefore, the most appropriate course of care for a POPF may be to secure anastomosis of the pancreas and digestive tract, followed with appropriate placement of a drain. Further, the management of DI may not adversely influence the outcomes of a POPF. Moreover, OC and UTI administration also have no notable effects on the patients' clinical course.

Data Availability

All data generated or analyzed during this study are included in this published article and are available from the corresponding author on reasonable request.

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