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Efficacy of Triple-Drug Therapy to Prevent Pancreatic Fistulas in Patients With High Drain Amylase Levels After Pancreaticoduodenectomy

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ABSTRACT

Backgrounds: Prior studies have suggested that drain amylase level is a predictive marker for developing pancreatic fistulas (PFs) after pancreaticoduodenectomy (PD). However, means of preventing PF after discovering high drain amylase levels have not been previously established. The purpose of this study was to evaluate the efficacy of a combination drug therapy (using three drugs; gabexate mesilate, octreotide, and carbapenem antibiotics, named as triple-drug therapy [TDT]) regimen in preventing PF for patients with high drain amylase levels on postoperative day (POD) 1 after PD.

Materials and methods: We divided the 183 patients who underwent PD into two groups in accordance with their enrollment in the study: for those enrolled early in the study (early period), TDT was not administered to patients with high drain amylase level; however, for those enrolled later in the study (late period), TDT was administered if drain amylase levels were over 10,000 IU/L on POD 1. We retrospectively compared the incidence of PF between the two groups.

Results: Incidences of PFs were statistically, significantly prevented in the late group (early 17% *versus* late 6%; $P = 0.01$). For patients with low levels of drain amylase (<10,000 IU/L), the PF ratio was equivalent between two groups (early 8% *versus* late 5%; $P = 0.56$); however, PFs in patients with high drain amylase levels in the late period group were dramatically prevented by TDT administration (early 89% *versus* late 11%; $P < 0.001$).

Conclusions: TDT may be a promising therapy to prevent PFs in patients with high drain amylase levels after PD.

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Introduction

Pancreatic fistulas (PFs) are a common but worrisome complication after pancreatic resection. PF often results in frequent drain replacement, a long hospital stay, or more fatal complications such as intraperitoneal bleeding due to pseudoaneurysm formation. Therefore, it is very important to both predict the risk of PF-based perioperative factors and to prevent their development.

The correlation between the duration of drain placement and the incidence of PF after pancreaticoduodenectomy (PD) has attracted a great deal of interest. Kawai *et al.*[1] reported that early drain removal on postoperative day (POD) 4 was effective for preventing PF compared with drain removal on POD 8. This conclusion was also supported by Bassi *et al.*[2] for patients with low drain amylase levels, the concentration of amylase in the drain fluid. Subsequently, long-term, prophylactic, drain insertion has been recognized as one of the risk factors for developing PFs because of the risk of intraperitoneal infection via the inserted drain, in other words, unnecessary drain placement would cause PF development.

In recent years, some authors have reported the significance of drain amylase levels after PD in predicting the development of PF.[3-6] The successful prediction of PF development using drain amylase levels has made it possible for clinicians to determine the appropriate timing of drain removal, thus decreasing the risk of PF development. However, it is not only important to predict the development of PFs but also to take action to prevent PFs in patients with high drain amylase levels. If we know the patients are at risk of developing PF in advance, preventive procedures should be taken before clinical PF occurs. In our previous study on distal pancreatectomy (DP) patients,[7] we concluded that early drain removal and triple-drug therapy (TDT) with gabexate mesilate, octreotide, and the antibiotic carbapenem, in patients at high risk of developing PF, were safe and effective for preventing PF. This research proved that drain placement after POD 1 was unnecessary for DP patients, and also indicated that TDT regime was effective in preventing PF in patients with high drain amylase levels (>10,000 IU/L). We have also confirmed the efficacy of TDT for PF prevention in animal experiments using a rat PF model.[8]

We have applied this TDT regime for patients with high drain amylase levels after PD in recent years. Therefore the purpose of this study was to find out the efficacy of triple-drug therapy after PD for patients with a high risk of developing PF.

Patients and methods

Patients

This was a retrospective study conducted at the Department of Surgery at Nagasaki University Hospital. Institutional review board approved this study (No. 12052800). From April 2007 to December 2016, 183 consecutive patients who underwent PD with pancreaticojejunostomy and received routine postoperative management were enrolled in this study. These patients were divided into two groups based on their enrollment date. For patients enrolled from April 2007 to February 2012 (the early period group), no additional treatments were performed, even if the patients had high drain amylase levels (≥10,000 IU/L on POD 1). On the other hand, for patients enrolled from March 2012 to December 2016 (the late period group), TDT was administered only for the patients with high drain amylase levels (≥10,000 IU/L on POD 1). The drains were removed on POD 5 unless there was infectious output. All other postoperative patient management was the same in both study periods as described in further sections.

Informed consent as to the operation and postoperative management was obtained preoperatively to the patients in both groups.

Operative procedure

The PD procedure was the same in both groups, as reported previously.[9] Subtotal gastric-preserving PD was performed during the entire study period. In the cases of portal invasion with invasive carcinoma of the pancreas head, portal vein reconstruction with end-to-end anastomosis was performed. Regarding this reconstruction, pancreatic anastomosis was performed using pancreaticojejunostomy with duct-to-mucosa anastomosis in all patients during the study period. In addition, a short 5Fr lost stent was inserted in all cases. All choledochojejunostomies were performed via retrocolic, and gastrojejunostomies via antecolic. Laparoscopic procedures were often performed for low-grade malignant tumors, such as intraductal papillary mucinous neoplasm, lower bile duct carcinoma, or ampullary carcinoma. Two closed suction drains were always placed near the anterior pancreas stump and they were pulled out from both sides of the abdominal wall.

Postoperative management

As with our previous DP study,[7] on the day of surgery, all patients were housed within the intensive care unit and usually moved to a ward on POD 1. Prophylactic antibiotic therapy using cefem was administered for 2 days, beginning with the day of surgery, as a standard clinical practice. No other medications with the potential to prevent PFs were administered. A low-fat diet was started on POD 3.

The drain amylase levels were measured on POD 1, 3, and 5 in both groups, and regardless of either the drain amylase levels or the amount of output, the drains were removed on POD 5 unless the output was infectious. If a purulent fluid was drained on POD 5, drainage management was continued until the purulent output disappeared.

TDT was administered to the patents with high drain amylase levels, in late period group only. The cutoff level for high drain amylase concentration was ≥10,000 IU/L, as in the previous DP study. As before,[7] three kinds of drugs were used for TDT: gabexate mesilate (600 mg/d as a continuous intravenous injection [c.i.v.]) as a proteolytic enzyme inhibitor, octreotide (300 μg/d c.i.v.) to reduce the pancreas' exocrine secretion, and carbapenem antibiotics (0.5 g/d intravenous injection [i.v.]) for bacteriostasis. One week after TDT initiation, if the patient's condition was unproblematic and serum

C-reactive protein (CRP) levels decreased sequentially, each drug was discontinued one by one. If the patient's condition was not improved by TDT, additional treatment such as drain reinsertion was performed.

Data analysis and definition

Both perioperative factors, including both patient and tumor characteristics, and operative outcomes were evaluated in this study. Postoperative complications were evaluated based on the Clavien-Dindo classification[10]; the definition of PF was based on the criteria of the International Study Group on Pancreatic Fistula,[11] that is, drain reinsertion or exchange even once were counted as grade B, and a grade of B/C was considered to represent PF in the present study. More specifically, intraperitoneal drain reinsertion or exchange and over 20 d of drainage were considered as PF grade B.

Study end points

To clarify the safety and efficacy of TDT after PD, the incidence of PF in patients with high drain amylase levels (≥10,000 IU/L) was set as a primary end point, and both postoperative complications and postoperative hospital stay were set as secondary end points.

Statistical analyses

Variables are described as either absolute numbers or median values and ranges. The Mann–Whitney U-test and Fisher's test were used for comparative evaluations between the two patient groups. For the multivariate analysis, quantitative variables were divided into two categories by their median values or its approximation and logistic regression analysis was performed. *P*-values <0.05 were considered significant. All statistical analyses were performed using Bell Curve for Excel version 2.00 (Social Survey Research Information Co, Ltd).

Results

The perioperative characteristics of the patients are summarized in Table 1. Because this was not a randomized study, some variables, such as laparoscopic operation rate or longer operative time due to high incidence of laparoscopic surgery, were only seen in early period group; there were no significant, statistical differences in other valuables between the two patient groups. Incidence of high drain amylase levels was 11% in early group and 17% in late group.

A comparison of the postoperative outcomes in all enrolled patients is summarized in Table 2. Serum white blood count (WBC), CRP, and the drain amylase levels were all statistically equivalent between the two groups. Regarding drain insertion duration, although the median value in both groups was the same, there were statistically significant differences between the two groups (actual average of insertion days in early period group was 10 and in late period group, it was 7). Both the occurrence rate of PF (early 17% *versus* late 6%, $P = 0.01$) and complication rates beyond Clavien-Dindo classification III a including PF, biliary fistula, chyle leakage, or colic perforation (early 32% *versus* late 19%, $P = 0.04$) were statistically improved in late period group because PF rate was decreased. Type C PF has not occurred in both of two groups. Drain tip culture positive rate in the patients with PF in late group was 50% (3/6 cases), not very high. The duration of hospital stay was equivalent between the two groups.

Table 3 summarizes the comparison of the operative results, especially in the patients with high drain amylase levels (≥10,000 IU/L on POD 1) in both groups. TDT was introduced to the patients only in the late period group. The number of patients included in each group in Table 3 corresponds to the patient number whose drain amylase levels were high in Table 1. Similar to Table 2, although serum WBC, CRP, and the drain amylase levels were statistically equivalent between the two groups, duration of drain insertion, occurrence rate of PF and complication and duration of hospital stay were

Table 1 – Preoperative and operative characteristics of the patients.

Variable	Early ($n = 81$)	Late ($n = 102$)	P-value
Age (y)	72 (35-86)	71 (31-87)	0.81
Invasive malignant tumor (%)	68/81 (84%)	82/102 (81%)	0.53
Diabetes mellitus (%)	29/81 (36%)	31/102 (30%)	0.44
Albumin (g/dL)	3.7 (2.5-4.9)	3.8 (2.8-5.0)	0.49
Laparoscopic surgery (%)	34/81 (42%)	10/102 (10%)	<0.001
Operative time (min)	601 (309-1050)	424 (270-845)	<0.001
Blood loss (mL)	900 (50-6650)	925 (50-5964)	0.75
Vascular resection (%)	11/81 (14%)	18/102 (17%)	0.45
Soft pancreas	51/81 (63%)	53/102 (52%)	0.16
WBC POD1 (× 103 mm^3)	11.1 (4.2-20.9)	10.7 (3.7-20.3)	0.12
CRP POD1 (mg/dL)	9.2 (2.7-26.8)	9.7 (4.0-16.0)	0.23
Drain amylase (IU/L) POD1	1150 (5-321,500)	819 (12-105,650)	0.66
Drain amylase ≥10,000 (IU/L)	9/81 (11%)	18/102 (17%)	0.22

IU/L = international unit per liter.

Table 2 – Comparison of the postoperative outcomes.

Variable	Early ($n = 81$)	Late ($n = 102$)	P-value
WBC POD 3 (× 103 mm^3)	7.9 (1.3-30.7)	7.9 (2.3-24.9)	0.88
POD 7	7.5 (2.7-30.5)	7.2 (1.1-22.3)	0.69
CRP POD 3 (mg/dL)	14.1 (2.9-32.3)	14.3 (2.4-35.8)	0.81
POD 7	5.0 (0.1-25.61)	5.3 (0.2-24.8)	0.97
Drain amylase (IU/L) POD 3	173 (2-17,968)	184 (1-33,803)	0.25
POD 5	44 (2-12,268)	28 (1-11,099)	0.13
Duration of drain insertion (d)	5 (5-60)	5 (5-81)	0.003
Drain tip culture	35/55 (64%)	71/98 (72%)	0.26
PF	14/81 (17%)	6/102 (6%)	0.01
Clavien-Dindo grade; beyond III a	26/81 (32%)	19/102 (19%)	0.04
Hospital stay (d)	24 (10-109)	23 (10-93)	0.98

IU/L = international unit per liter.

statistically improved in the late period group. In the early period group, without TDT, almost all cases with high amylase levels developed PF (8 of 9, 89%); however, incidences of PF were decreased by treating patients with high amylase levels with TDT in the late group (only 2 of 18 patients developed PF, 11%). During the TDT, none of toxicity or adverse effect by which we forced to stop or decrease the treatment had occurred in the patients treated with TDT during the study period. However, there is a possibility that we could not measure any adverse effect in blood test or minute symptom occurred by TDT. Table 4 shows the occurrence rate of PF when the drain amylase levels were higher or lower than 10,000 IU/L. As previously described, there were no statistical differences in the patients with drain amylase levels under 10,000 IU/L; however, in patients with drain amylase levels over 10,000, there was statistically significant difference between the two groups due to the administration of TDT.

Discussion

The prevention of PFs, especially in the patients with high drain amylase levels after PD, was successfully achieved by TDT in the present study. The efficacy of TDT in preventing PF was similar to our previous DP study.[7] However, there are two major differences between the previous DP study and the present PD study.

First, drain removal occurred on POD 1 in the DP study and on POD 5 in the present PD study. Although it is well recognized that long-term insertion of a prophylactic drain after pancreatic resection should be avoided, there have been no definitive conclusions regarding the merits and demerits of early drain removal (including no drain insertion) after PD. Mehta *et al.*,[12] based on their retrospective results, concluded that the placement of closed suction drains after PD did not appear to decrease the rate of either secondary drainage procedures or reoperations, and might be associated with both increased PF and overall morbidity. Conlon *et al.*[13] suggested that closed suction drainage should not be considered mandatory or even standard after pancreatic resection because the mortality and morbidity rates were the same between the two groups in their randomized controlled trial with early drain removal. Correa-Gallego *et al.*[14] also reported that operative drains were associated with a longer hospital stay and higher rates of morbidity, fistula, and readmission, and did not decrease the need for either reintervention or

Table 3 – Comparison of the postoperative outcomes in the patients with drain amylase ≥10,000 IU/L.

Variables	Early ($n = 9$, 11%)	Late ($n = 18$, 17%)	P-value
WBC POD 3 (× 10^3 mm^3)	8.7 (4.5-13.9)	9.8 (4.1-17.7)	0.44
POD 7	7.7 (2.7-12.0)	6.5 (4.3-11.3)	0.44
CRP POD 3 (mg/dL)	25.1 (11.5-32.4)	18.3 (4.5-35.8)	0.06
POD 7	10.2 (3.6-25.6)	6.4 (0.3-19.0)	0.12
Drain amylase (IU/L) POD 3	1446 (119-17,968)	1947 (76-33,803)	0.80
POD 5	488 (24-12,268)	513 (11-11,099)	0.82
Drain tip culture	6/7 (86%)	10/17 (59%)	0.43
Duration of drain insertion (d)	24 (5-60)	5 (5-25)	<0.001
PF	8/9 (89%)	2/18 (11%)	<0.001
Clavien-Dindo grade; beyond III a	8/9 (89%)	4/18 (22%)	0.004
Hospital stay (d)	43 (14-71)	30 (16-43)	0.04

IU/L = international unit per liter.

Table 4 – Comparison between two groups regarding the incidence of PF.

Variable	Early ($n = 81$)	Late ($n = 102$)	P-value
Drain amylase level < 10,000 IU/L	6/72 (8%)	4/84 (5%)	0.560
≥10,000 IU/L	8/9 (89%)	2/18 (11%)	<0.001
All patients	14/81 (17%)	6/102 (6%)	0.01

IU/L = international unit per liter.

mortality rates. In addition, Witzigmann *et al.*,[15] based on their RCT, concluded that the omission of drains was not inferior to intra-abdominal drainage in terms of postoperative intervention and was superior in terms of both clinically relevant PF rate and fistula-associated complications. By contrast, Van Buren *et al.*[16] reported that their Data Safety Monitoring Board stopped the study early because of an increase in mortality from 3% to 12% in the patients undergoing PD without intraperitoneal drainage. Previously we also conducted a similar comparison regarding drain insertion and concluded that prophylactic drainage was helpful in various situations in the early postoperative days (data not shown). Therefore, we conducted the present study with drain removal on POD 5, and we recommend placing the drains after PD for at least a few days to evaluate the drain amylase levels.

Another difference is that our previous DP study resulted in the complete prevention of PFs via early drain removal, which differed from the results of the present study (of course we think that 6% occurrence rate in late period is sufficiently acceptable). We assume that this discrepancy is caused by the rates of intraperitoneal infection with anastomosis of the digestive tract in PD patients. A past report suggested that bacterial contamination in ascitic fluid might be an initiating event that leads to the development of clinical PF, and concluded that both the administration of appropriate antibiotics and early drain removal were important for the prevention of PF.[17] Actually, there was a high incidence rate of positive drain tip culture in the present study (early period, 64%; late period, 72%; summarized in Table 2), indicating the presence of intraperitoneal bacterial contamination. Thus, we may have to take additional measures to control the intraperitoneal bacterial contamination. TDT would be effective for intraperitoneal bacterial management because the drain tip culture positive rate and the rate of PF itself were both decreased in the patients with high drain amylase levels in late period group.

There have been several articles that discuss the usefulness of preoperative factors for predicting PF risk[18-20]; however, even if PF is predicted, the surgery itself is still necessary and, therefore, prediction using preoperative factors is not clinically useful. On the other hand, most past reports, which were evaluating the prediction of PF, mostly concluded drain amylase level as an excellent predictor;[1,2,21] therefore, we also used the drain amylase level over 10,000 IU/L as a cutoff value to introduce TDT in the present study. With respect to other possible predictors in the recent literatures, although there are reports that described the efficacy of a combination of drain amylase level and CRP,[22] or a combination of drain amylase, WBC, and fever up,[23] there are few articles mentioning other than drain amylase level. Therefore, for the time being, it would be the only way to evaluate the drain amylase level as a postoperative PF indicator after PD.

We have already performed rat PF experiment and also discussed the efficacy of TDT.[8] The aim of using each drug in TDT is that gabexate mesilate, which is a proteolytic enzyme inhibitor, is expected to suppress pancreas exocrine activity; octreotide, which could reduce the pancreatic exocrine secretion; and carbapenem antibiotics are expected to carry out bacteriostasis in intraperitoneal fluid collection. There also have been clinical past reports in the literature regarding the prevention of PF development using certain drugs; however, the efficacy of the drugs in each report has been ambiguous. Uemura *et al.*[24] described that prophylactic administration of ulinastatin reduced both the serum and drain amylase levels, and the incidence of postoperative pancreatitis after PD; however, there was no significant difference in the incidence of PF with or without ulinastatin administration. Gans *et al.*[25] indicated in their review of the literature that there was no solid evidence that somatostatin analogs result in a higher closure rate of PF compared with other treatments. On the other hand, Allen *et al.*[26] conducted the RCT to clarify the efficacy of pasireotide in preventing PF development and concluded that perioperative treatment with pasireotide decreased the rate of PF. In addition, Denbo *et al.*[27] concluded that selective administration of pasireotide only to patients with a high risk of PF might maximize the cost-efficacy of prophylactic pasireotide, based on the cost estimation in accordance with risk prediction. In the present study, as Denbo *et al.* described, the preventing effect of TDT for PF would be caused the patients selection to receive TDT in accordance with their risk of developing PF, whether their drain amylase levels were high or not. To the best of our knowledge, this is the first study describing the efficacy of a drug therapy in which treated patients were limited to high-risk cases of PF. As stated by the International Study Group of Pancreatic Surgery,[28] "future studies which focus on novel approaches to decrease the rate of PF should be conducted based on the appropriate risk evaluation".

There are some major limitations in the present study. First, this was retrospective, single institutional study, so that the number of patients was small and some background deviations were detected. Further randomized and multi-institutional investigations for evaluating the efficacy of this treatment are necessary to prove the present results. Second, the TDT regimen in the present study requires 1 wk of fasting, even though the patient's condition was healthy in almost cases. Fujii *et al.*,[29] based on their multi-institutional study, concluded that food intake neither aggravated PF, nor prolonged either the length of drain placement or hospital stay after PD. Therefore, it might be possible to administer TDT without fasting, which would be better for the patients. In the future, we will be testing further improvements to our TDT protocol.

In conclusion, we found that TDT might be an effective treatment to prevent PFs in patients with high drain amylase levels after PD surgery in late period. Based on our findings, regardless of preoperative predictive factors of PF, it may be

possible to prevent PF by TDT after PD. Randomized trial should be conducted to clarify the evidential effectiveness of TDT.

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Disclosure

The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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