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Title:

Efficacy of triple-drug therapy to prevent pancreas fistulas in patients with high drain amylase levels after pancreaticoduodenectomy.

Short title: Triple-drug therapy after PD

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Conflict of interests

Every authors have no conflict of interests as to this manuscript

Abstract

Backgrounds: Prior studies have suggested that drain amylase level is an predictive marker for developing pancreas fistulas (PF) 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 drug; gabexate mesilate, octreotide, and carbapenem antibiotics, named 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 PF were statistically, significantly prevented in the late group (early; 17% vs. 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% vs. late 5%; p=0.56), however PF in patients with high drain amylase levels in the late period group were dramatically prevented by TDT administration (early; 89% vs. late 11%; p＜0.001).

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

Key words: PD, PF, TDT, drain amylase level

INTRODUCTION

Pancreatic fistulas (PF) 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 peritoperative 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.* (5) reported that early drain removal on postoperative day (POD) 4 was effective for preventing PF compared to drain removal on POD 8. This conclusion was also supported by Bassi et *al.* (6) 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 PF 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 pancreaticoduodenectomy (PD) in predicting the development of PF (1-4). 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 PF but also to take action to prevent PF 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 treatment 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 pancreticojejunostomy 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 2007/04 to 2012/02 (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 2012/03 to 2016/12 (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 (SSPPD) 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, pancreas anastomosis was performed using pancreaticojejunostomy with duct-to mucosa anastomosis in all patients during the study period. Additionally, a short 5fr lost stent was inserted in all cases. All choledochojejunostomies were performed via retro-colic, and gastrojejunostomies via ante-colic. Laparoscopic procedures were often performed for low-grade malignant tumors, such as intraductal papillary mucinous neoplasm (IPMN),

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 house within the intensive-care unit and usually moved to a ward on POD 1. Prophylactic antibiotic therapy using cefem was administered for two days, beginning with the day of surgery, as a standard clinical practice. No other medications with the potential to prevent PF 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 cut off level for high drain amylase concentration was ≧10,000IU/L, as in the previous DP study. As before (7), three kinds of drugs were employed for TDT: gabexate mesilate (600 mg/day as a continuous intravenous injection (c.i.v.)) as a prorphyractic enzyme inhibitor, octreotide (300 μg/day c.i.v.) to reduce the pancreas' exocrine secretion, and carbapenem antibiotics (0.5 g/day intravenous

injection (i.v.)) for bacteriostasis. One week after TDT initiation, if the patient 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 re-insertion 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 (ISGPF) (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 re-insertion or exchange, and over 20 days 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 endpoint, and both postoperative complications and postoperative hospital stay were set as secondary endpoints.

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 BellCurve 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 was 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, though the median value in both groups was the same, there were statistically significant differences between the two groups (actual average

insertion days in early period group was 10 and in late period group was 7). Both the occurrence rate of PF (early 17% vs. late 6%, p=0.01) and complication rates beyond Clavien-Dindo classification IIIa including PF, biliary fistula, cyle leakage or colic perforation (early 32% vs. 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 patents 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, though 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 statistically improved in the late period group. In the early period group, without TDT, almost all cases with high amylase levels developed PF (8 out of 9, 89%), however incidences of PF were decreased by treating patients with high amylase levels with TDT in the late group (only 2 out of 18 patients developed PF, 11%). During the TDT treatment, none of toxicity or adverse effect by which we forced to stop or decrease the treatment were not occurred in the patients 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 PF, 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 mortality rates. Additionally, 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 pancreatic fistula rate and fistula-associated complications. In 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 (date 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 PF 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 papers 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, the majority of past reports which evaluating the prediction of PF were mostly concluded that drain amylase level as an excellent predictor (5,6,21), therefore we also employed the drain amylase level over 10,000 IU/L as a cut off value to introduce TDT in the present study. With respect to other possible predictors in the recent literatures, though 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 papers 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 using each drugs in TDT is that gabexate mesilate which is proteolytic enzyme inhibitor is expected the suppression of pancreas exocrine activity, octreotide which could reduce the pancreas exocrine secretion, and carbapenem antibiotics is expected 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 following 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 analogues 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 week 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 PF 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 treatment after PD surgery. Randomized trial should be conducted to clarify the evidential effectiveness of TDT.

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Table 1. Preoperative and operative characteristics of the patients

Variable	early (n=81)	late (n=102)	*p*- value
age (years)	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 mm3)	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	1,150 (5-321,500)	819 (12-105,650)	0.66
drain amylase ≧10,000 (IU/L)	9/81 (11%)	18/102 (17%)	0.22

WBC; white blood cell, POD; post operative day, CRP; C-reactive protein, IU/L; international unit per litter

Table 2. Comparison of the postoperative outcomes

Variable	early (n=81)	late (n=102)	*p*- value
WBC POD3 ($\times 10^3$ mm^3)	7.9 (1.3–30.7)	7.9 (2.3–24.9)	0.88
POD7	7.5 (2.7–30.5)	7.2 (1.1-22.3)	0.69
CRP POD3 (mg/dL)	14.1 (2.9–32.3)	14.3 (2.4–35.8)	0.81
POD7	5.0 (0.1–25.61)	5.3 (0.2–24.8)	0.97
drain amylase (IU/L) POD3	173 (2-17,968)	184 (1-33,803)	0.25
POD5	44 (2–12,268)	28 (1-11,099)	0.13
duration of drain insertion (days)	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 (days)	24 (10–109)	23 (10–93)	0.98

WBC; white blood cell, POD; post operative day, CRP; C-reactive protein, IU/L; international unit per litter, PF; pancreatic fistula

Table 3. Comparison of the postoperative outcomes in the patinets with drain amylase≧ 10,000

Variables	early (n=9, 11%)	late (n=18, 17%)	*p*- value
WBC POD3 ($\times 10^3$ mm^3)	8.7 (4.5–13.9)	9.8 (4.1–17.7)	0.44
POD7	7.7 (2.7–12.0)	6.5 (4.3-11.3)	0.44
CRP POD3 (mg/dL)	25.1 (11.5–32.4)	18.3 (4.5–35.8)	0.06
POD7	10.2 (3.6–25.6)	6.4 (0.3–19.0)	0.12
drain amylase (IU/L) POD3	1,446 (119-17,968)	1,947 (76-33,803)	0.80
POD5	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 (days)	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 (days)	43 (14–71)	30 (16–43)	**0.04**

WBC; white blood cell, POD; post operative day, CRP; C-reactive protein, IU/L; international unit per litter, PF; pancreatic fistula

Table 4. Comparison between two groups in regarding the indidence of PF.

Variable	early (n=81)	late (n=102)	*p*- value
drain amylese level＜ 10,000 IU/L on POD1	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 litter,