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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