

## Original article

## Safety and efficacy of early drain removal and triple-drug therapy to prevent pancreatic fistula after distal pancreatectomy



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## ABSTRACT

**Objective:** Prior studies suggested that early drain removal prevented the development of pancreatic fistula (PF) after pancreaticoduodenectomy (PD), but there has been no corresponding prospective trial for distal pancreatectomy (DP). The purpose of this study was to determine the safety and efficacy of early drain removal and triple-drug therapy (TDT) with gabexate mesilate, octreotide and carbapenem antibiotics to prevent PF after DP in patients at high-risk of developing PF.

**Methods:** A total 71 patients who underwent a DP were enrolled. We prospectively divided them into two groups: the late-removal group, in which the drain remained in place for at least for 5 days post-operatively ( $n = 30$ ) and the early-removal group in which the drain was removed on postoperative day 1 (POD1) ( $n = 41$ ). For the patients with a high drain amylase level ( $\geq 10,000$  IU/L) and patients with symptomatic intraperitoneal fluid collection, our original TDT was introduced. The primary endpoint was the safety and efficacy of this management, and the secondary endpoint was the incidence of PF.

**Results:** The incidence of clinical PF was significantly lower in the early-removal group (0% vs. the late removal 16%;  $p < 0.001$ ). In the early-removal group, TDT was administered to 12 patients (29%) and none of the patients needed additional treatment after TDT.

**Conclusions:** Postoperative management after DP with early drain removal and TDT was safe and effective for preventing PF.

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## Introduction

Distal pancreatectomy (DP) is generally performed for benign and malignant tumors of the left side of the pancreas. Several operative procedures for these tumors have been developed over the past 20 years, including the use of spleen preservation [1] and laparoscopic surgery [2]. However, the incidence of the most common and most serious postoperative complication after DP, postoperative pancreatic fistula (PF), was not found to be improved in several clinical prospective trials [3–5]. It is apparent that a radical change in postoperative management is necessary to prevent PF after DP.

Kawai et al. [6] reported the efficacy of early drain removal to prevent PF after pancreaticoduodenectomy (PD) for pancreas-head disease, and Bassi et al. [7] followed the early drain removal method and obtained the same results. Kawai et al. speculated that the reason for these favorable results is that there is a close association between infection via an inserted drain and subsequent PF development, and long-term drain insertion might cause intraperitoneal infections, including PF [6]. In light of these results, it seems that prophylactic long-term drain insertion after PD is not ideal, and that it may be possible to prevent PF by early drain removal. However, to the best of our knowledge, prospective trials of early drain removal to prevent PF have not been conducted. The present prospective study was conducted to clarify whether PF after DP can be prevented by early drain removal.

Two groups reported that the incidence rate of PF after DP was higher than that after PD [8,9]. This finding implies that early drain removal could also be the cause of an increase of intraperitoneal

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abscess or intraperitoneal bleeding due to the rupture of a pseudoaneurysm. To reduce such an assumptive risk in the present study, we introduced an original triple-drug therapy (TDT) for high-risk patients whose drainage fluid had a high amylase level (i.e., a high drain amylase level) on postoperative day 1 (POD1) or any unusual symptom associated with intraperitoneal fluid collection after drain removal. The purpose of this study was to determine the safety and efficacy of the early drain removal and TDT to prevent PF after DP in high-risk PF patients.

## Patients and methods

### Patients

This was a prospective study conducted at the Department of Surgery, Nagasaki University Hospital. The study design and protocol were approved by the Institutional Review Board at our hospital. From June 2005 to April 2013, 79 DP procedures were performed in our department, and we divided the patients into two groups according to the day of drain removal as follows: the late-removal group, who underwent a DP in the period from June 2005 to September 2009, during which the drains were inserted for at least postoperative 5 days, and the early-removal group, who underwent a DP in the period from October 2009 to April 2013, during which the drain in all cases was removed on POD1 (Fig. 1).

Of the 33 patients in the late-removal group, three patients were excluded from the present study due to the combined resection of the remnant pancreas (one patient each because of pancreas head resection with a second portion of duodenectomy, duodenum-preserving pancreas head resection, and uncinectomy). Of the 46 patients in the early-removal group, five patients were excluded: combined with other-organ resection (one patient each for the colon and left kidney), one patient with uncinectomy of the remnant pancreas, and two patients because of postoperative intraperitoneal bleeding via the drain on the day of surgery. Thus a total of 30 patients in the late-removal group and 41 patients in the early-removal group were enrolled.

### Operative procedure

Different types of DP procedures were performed in the study period. Spleen preservation and laparoscopic surgery were often performed for the low-grade malignant tumors such as intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic

neoplasm (MCN). For invasive ductal carcinoma, DP by means of laparotomy with splenectomy and lymph node dissection was always performed. For the pancreas stump closure, approx. one-half of the cases were transected by stapler (Endo GIA™ 60-mm Articulating Medium/Thick Reload with Tri-Staple™ Technology, Covidien, Mansfield, MA, USA) and the other half were closed by the fish mouse technique or gastric wall covering [10]. A closed suction drain was always placed near the pancreas stump and pulled out from the patient's left-side abdominal wall.

### Postoperative management

On the day of surgery, all patients were controlled in the intensive-care unit and then moved to the general ward on POD1. Prophylactic antibiotics therapy by using the cefem was administered for three days including the day of surgery as a standard clinical practice. No other medicine which had the possibility to prevent PF was administered.

The drain amylase level was measured on POD1, 3, and 5 in the late-removal group, and on only POD1 in the early-removal group. In the late-removal group, the drain was removed unless clearly purulent fluid was drained on POD5, regardless of the drain amylase level or the amount of output. If purulent fluid was drained before POD5, drainage management was continued until the purulent output disappeared. In the early-removal group, the drain was always removed on POD1, regardless of the drain amylase level or amount of output.

TDT with gabexate mesilate (600 mg/day as a continuous intravenous injection [c.i.v.]), octreotide (300 µg/day c.i.v.) and antibiotic; carbapenem (0.5 g/day intravenous injection [i.v.]) antibiotics was administered to late-removal group patients with a high drain amylase level ( $\geq 10,000$  IU/L) on POD1, 3, or 5 and to early-removal group patients with a high drain amylase level ( $\geq 10,000$  IU/L) on POD1, and to patients who had developed any clinical symptoms (e.g., a fever  $\geq 38$  °C, abdominal pain or fullness) with the intraperitoneal fluid collection after drain removal. According to the antibiotic, carbapenem was employed for this study based on the results of the bacterial sensitivity of the drain tip culture after PD in our department (data not shown). Intraperitoneal fluid collection was confirmed by enhanced computed tomography (CT) or ultrasound (US). After the disappearance of clinical symptoms and a tendency for the patient's serum C-reactive protein (CRP) to decrease were confirmed, the patient's diet was restarted and the components of the TDT were discontinued one by one (Fig. 2). If the patient's condition was not improved by the TDT, additional treatment such as drain re-insertion or relaparotomy was performed.

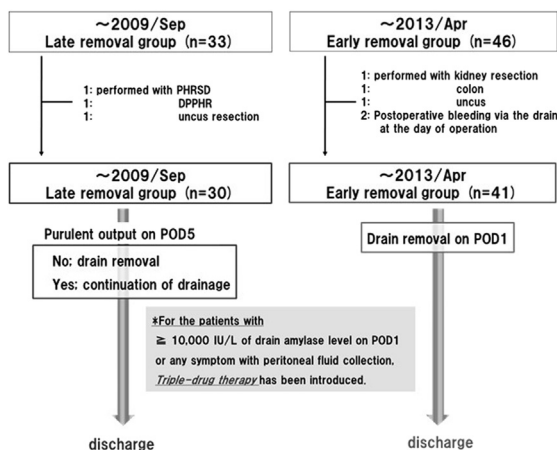


Fig. 1. Patients flow of this study. PHRSD: Pancreas head resection with segmental duodenectomy, DPPHR: Duodenum preserved pancreas head resection.

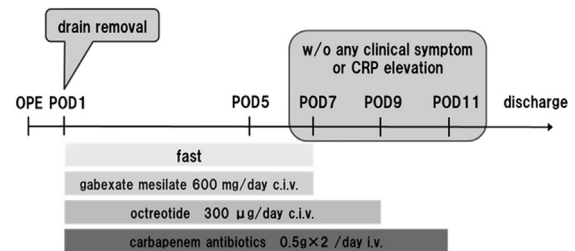


Fig. 2. TDT for high drain amylase levels (over 10,000 IU/L) in the early-removal group. TDT was introduced from POD1, and after confirmation of the absence of any clinical unusual symptom and the decrease of the patient's serum CRP level after POD7, the TDT components were omitted one by one. POD: postoperative day, c.i.v.: continuous intravenous injection, i.v.: intravenous injection.

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