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Original article

Rapid postoperative reduction in prognostic nutrition index is associated with the development of pancreatic fistula following distal pancreatectomy

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ABSTRACT

Backgrounds: Despite recent advances in surgical techniques and devices for pancreatic remnant closure, postoperative pancreatic fistula (POPF) still remains one of the common complications after distal pancreatectomy (DP). Identification of risk factors for POPF may lead to the development of new strategies to prevent this ominous complication.

Methods: We retrospectively reviewed data on 44 patients undergoing DP with the use of a stapler to identify risk factors for POPF. Study variables included preoperative prognostic nutritional index (PNI) and reduction rate of PNI on postoperative day (POD) 7.

Results: POPF occurred in 23 patients (52%), of which 13 (56%) were grade B or C. Univariate analyses comparing patients with POPF and those without POPF showed significant differences in body mass index ($P = 0.0102$), pancreatic thickness ($P = 0.0134$), white blood cell count on POD7 ($P = 0.0432$), C-reactive protein level on POD7 ($P = 0.0123$), and PNI reduction rate ($P = 0.0471$). A multivariate analysis revealed pancreatic thickness ($P = 0.0121$) and PNI reduction rate ($P = 0.0165$) to be significant factors for POPF. Furthermore, the PNI reduction rate was significantly higher in patients with clinically relevant (grade B/C) POPF than in those with no or grade A POPF ($P = 0.0257$). In most patients, the massive postoperative PNI reduction preceded the diagnosis of clinically relevant POPF.

Conclusions: These findings suggest that rapid postoperative reduction in PNI is associated with the development of POPF.

1. Introduction

Despite continued efforts to prevent postoperative complications after pancreatic resection, postoperative pancreatic fistula (POPF) still represents one of the most common and major complications. The incidence of POPF after distal pancreatectomy (DP) has been reported to range from 30 to 50% in most recent series [1–4]. Although POPF can be managed in most patients by conservative or, occasionally, invasive interventions, it may result in potentially life-threatening complications, such as intraabdominal abscess and massive hemorrhage [5]. There is a desperate need for improved strategies to prevent this complication.

Previous reports described risk factors for POPF after DP, including older age, increased weight/body mass index (BMI), malnutrition, diabetes, previous laparotomy, thick pancreas, extensive lymphadenectomy, longer operative time, and increased blood loss during surgery [1,2,6–10]. Furthermore, closure techniques of the pancreatic remnant have been reported to affect the incidence of POPF after DP [1,11–14]. In particular, many studies have addressed the optimal techniques of stapled closure of the pancreatic remnant to prevent POPF [12,15–17]. However, even with the improved surgical techniques, the rate of POPF has remained essentially unchanged [18], implying the importance of controlling other risk factors, such as those related to patient's comorbidities and nutritional status.

In 2008, we introduced a technique of staple closure of the pancreatic remnant in DP. However, a significant proportion of

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patients were found to develop POPF after the introduction of stapled DP. In an attempt to identify risk factors, especially patient-related factors, for the development of POPF, we used univariate and multivariate analyses to investigate clinical variables in patients undergoing DP with a stapler.

2. Patients and methods

2.1. Patients

Between June 2008 and March 2013, a total of 44 patients underwent DP with the use of a stapler for benign and malignant indications in the Department of Surgery 1 at University of Occupational and Environmental Health (Kitakyushu, Japan). They included 15 men and 29 women with a mean age of 68 years (range, 30–90 years). Indications for surgery included pancreatic adenocarcinoma ($n = 20$), intraductal papillary mucinous neoplasm (IPMN; $n = 10$), solid pseudopapillary tumor ($n = 3$), serous cystic neoplasm ($n = 3$), lymphoepithelial cyst ($n = 2$), and others (metastatic renal cell carcinoma, aberrant spleen, mucinous cystic neoplasm, neuroendocrine tumor, retention cyst, and sarcoidosis of the pancreas; $n = 1$ for each).

2.2. Operative procedure and postoperative management

DP for malignant tumors includes resection of the left-sided pancreas along with the resection of the spleen and standard lymphadenectomy. In patients with benign pancreatic disorders, the spleen and, in most instances, the splenic vessels are preserved. DP was performed via laparotomy in 38 patients and via laparoscopic approach in the remaining 6 patients. The transection line of the pancreas was determined based on the location and pathology (malignant or benign) of the lesion. For malignant tumors, the pancreas is usually divided above the superior mesenteric vein (SMV)/portal vein trunk or at the pancreatic neck (extended distal pancreatectomy) in some cases where a tumor is located close to the pancreatic head. For benign or borderline pancreatic lesions, the transection line is usually set at 3-cm proximal to the lesion to preserve the normal pancreatic parenchyma. Transection of the pancreatic parenchyma was done using a linear stapler (Echelon 60, Ethicon Endo-Surgery, Cincinnati, OH, USA) which provides simultaneous closure of the pancreatic remnant. To avoid traumatic splits of the pancreatic parenchyma, we used a technique of slow gradual closure, compression, and firing of the stapler, spending approximately 10 min for each process, as described previously [15,16].

Drainage tubes are placed in the left subphrenic space and in the vicinity of the pancreatic remnant. These tubes are drained to the outside of the abdomen and fluids from both drains were collected for measurements of amylase level on postoperative days (POD) 3, 7, and thereafter where necessary. Total parental nutrition (TPN) was not routinely performed. In some patients who were diagnosed to have POPF or those who were expected to require fasting for a while, TPN was performed (usually starting on POD 4 or thereafter) according to the surgeon's decision. None of the patients received enteral nutrition in the early postoperative period (within POD 7). An oral diet is restarted, in most patients, on or after POD 7 if there is no evidence of POPF or other major postoperative complications. The intraabdominal drains were removed between POD7 and POD14, based on a decision of the attending surgeon.

2.3. Postoperative pancreatic fistula and clinical variables for risk factor analysis

The diagnosis of POPF was made by drain output of any measurable volume of fluid on or after POD 3 with amylase content 3 times greater than serum amylase activity, according to the International Study Group for Pancreatic Fistula (ISGPF) [19]. POPF was classified as follows: grade A, a transient, asymptomatic fistula with only elevated drain amylase levels and treatments or deviation in clinical management are not required; grade B, a symptomatic, clinically apparent fistula requiring diagnostic evaluation and therapeutic management; and grade C, a severe, clinically significant fistula requiring a major deviations in clinical management and unequivocal aggressive therapeutic interventions [19].

The clinical variables analyzed for the correlation with POPF were as follows: age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) score, preoperative prognostic nutritional index (PNI), indication for surgery (pancreatic adenocarcinoma or others), the use of laparoscopy, resection line (on and proximal to the SMV versus distal to the SMV), dilatation of the main pancreatic duct (defined as a diameter of the MPD greater than 5 mm on preoperative CT at the resection line described in the operation record), pancreatic thickness (measured on preoperative CT at the resection line described in the operation record), operative time, intraoperative blood loss, white blood cell (WBC) counts on POD7, C-reactive protein (CRP) on POD7, and postoperative reduction rate of PNI. The PNI was calculated as $10 \times$ serum albumin (g/dl) $+ 0.005 \times$ total lymphocyte count (per mm^3) [20]. The reduction rate of PNI was defined as a percentage of decrease in the PNI on POD 7.

2.4. Data presentation and statistical analysis

All values for the pancreatic thickness, intraoperative blood loss, and PNI reduction rate were shown as means $\pm$ standard deviations. Statistical analyses were done using JMP 10 software (SAS Institute Inc., Cary, NC, USA). Categorical variables were analyzed using the Fisher's exact probability test and continuous variables were analyzed using the Mann–Whitney U test. Multivariate analysis was done for all variables with P-values of less than 0.2 by univariate analysis using a logistic regression analysis. A P-value of less than 0.05 was considered statistically significant.

3. Results

Overall, POPF occurred in 23 of 44 patients (52%). The POPF was classified as grade A in 10 patients and grade B in 13 patients. Therefore, clinically relevant (grade B/C) POPF occurred in 13 patients (30%). The timing of diagnosis of clinically relevant POPF varied from POD 4 to 24 (median of 11). There was only one patient who developed clinically relevant POPF before POD7 (on POD4). In the other 12 patients, however, the diagnosis of clinically relevant POPF was made on and after POD 7. We started treatment for POPF, including fasting, antibiotics, and/or additional drainages, immediately after the diagnosis of POPF.

Other complications included intraabdominal abscess, liver abscess, acute cholecystitis, and chylous ascites (1 patient for each). There was no 30-day mortality in this series.

3.1. Comparison of clinical variables between patients with POPF and those without POPF

We compared clinical variables between patients with POPF ($n = 23$) and those without POPF ($n = 21$) (Table 1). There were no differences in age, gender, ASA score, indication for surgery, the use of laparoscopy, resection line, main pancreatic duct dilatation, and operative time. The amount of intraoperative blood loss tended to be larger in patients with POPF than in those without POPF (340 ± 310 mL vs 244 ± 350 mL), though the difference did not reach a statistical significance ($P = 0.0779$). Overweight (BMI ≥ 25)