Comparison of Outcomes with Hand-sewn *Versus* Stapler Closure of Pancreatic Stump in Distal Pancreatectomy

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Abstract. *Aim: The optimal method for pancreatic stump closure to prevent postoperative pancreatic fistula (POPF) after distal pancreatectomy (DP), remains controversial though DP is still the only curative treatment for pancreatic cancer and other malignancies located on pancreatic body or tail. Patients and Methods: A total of 44 patients who consecutively underwent open DP were retrospectively analyzed, dividing them into two groups: group H (hand-sewn; n=24) and group S (stapler closure; n=20). Results: POPFs were encountered in 5 (21%) and 11 (55%) patients in groups H and S, respectively ($p=0.02$). POPFs of Clavien–Dindo grade IIIa or above were observed in two (8%) and seven (35%) patients in groups H and S, respectively ($p=0.03$). Conclusion: When indicating stapler closure, caution should be exercised for pancreatic consistency and thickness, device and cartridge type, and pancreatic duct ligation to more effectively control POPF rates.*

Distal pancreatectomy (DP), performed for removing pancreatic lesions located to the left of the superior mesenteric vein, accounts for approximately 25% of all pancreatic resections (1). Most recently reported overall mortality rate of DP is less than 3% (2). However, albeit technically simpler to perform than pancreaticoduodenectomy, morbidity rate of DP remains substantial.

Postoperative pancreatic fistulas (POPFs), which may result in numerous clinically-significant and potentially life-threatening complications such as intra-abdominal abscess and hemorrhage and surgical site infection, is the leading cause of morbidity after DP, with an incidence of

approximately 30-60% (2-7). Risk factors associated with POPFs after DP include decreased serum albumin levels, concurrent splenectomy, increased body weight, increased duration of surgery, higher American Society of Anesthesiologists score, and impaired renal function (3, 4, 8). Furthermore, POPFs often translate to significant increases in hospitalization costs (9). Thus, development of optimal and cost-effective pancreatic stump closure strategies to prevent POPF formation has been a topic of intense investigation. A number of interventions, such as sealing of the pancreatic duct stump with glue (10) or BioGlue (11), use of perioperative octreotide, and variations in surgical techniques have been advocated to reduce the incidence of POPF formation. However, optimal method of pancreatic stump closure remains controversial.

The primary aim of this retrospective, single-institution study was to compare the incidence of POPF after DP using two most commonly preferred pancreatic stump closure techniques, stapler *versus* hand-sewn closure, in a clinical setting. In addition, risk factors associated with POPF formation after DP using these two approaches were determined.

Patients and Methods

Patients. This study was approved by the Institutional review board of the Jikei University School of Medicine in October, 2015. A total of 44 patients who consecutively underwent open DP for various indications between April 2009 and October 2014 at Jikei University School of Medicine in Japan were included in this study. Patients were categorized into two groups according to the pancreatic stump closure technique: hand-sewn (group H, n=24) and stapler (group S, n=20). As shown in Table I, there were no differences in pre-operative characteristics such as sex, age, and primary indication for DP between the two groups. In both groups, pancreatic carcinoma was the predominant indication for DP in more than 50% of the patients. Both groups included patients with pancreatitis, all of whom were preoperatively diagnosed as malignant.

Patient assessment. Patient information during preoperative, intraoperative, and postoperative periods, stored in an electronic

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Key Words: Post-operative pancreatic fistula, distal pancreatectomy, hand-sewn closure, stapler closure.

Table I. Patient characteristics.

	Group H (N=24)	Group S (N=20)	p-Value
Age (years) (range)	62.0 (27-81)	69.5 (41-80)	0.11
Gender (Male/Female)	16/8	14/6	0.81
Diabetes mellitus	9 37.5	11 55.0	0.25
Serum albumin (g/dl)	4.2±0.4	4.0±0.4	0.28
Indication			0.53
Pancreatic cancer	12, 50.0	14, 70.0	
Neuroendocrine tumor	6, 25.0	3, 15.0	
IPMN	3, 12.5	1, 5.0	
Pancreatitis	2, 8.3	1, 5.0	
MCN	1, 4.2	0	
Metastatic carcinoma	0	1, 5.0	
Concomitant pancreatitis	4 16.7	6 30.0	0.29
Pancreatic thickness on the transection line (mm)	12.9±5.0	11.6±3.9	0.35

n%, Median [min-max], mean±standard deviation. IPMN: Intraductal papillary mucinous neoplasm, MCN: mucinous cystic neoplasm.

medical database, was retrospectively analyzed. The primary outcome of this study was to compare the incidence of POPF after DP with two pancreatic stump closure: hand-sewn and stapler closure. Secondary outcomes were comparison of perioperative outcomes between the two closure techniques and identification of factors associated with POPFs classified as Clavien–Dindo grade IIIa or above (12). Parameters evaluated as potential risk factors for POPF were age, sex, diabetes mellitus, preoperative serum albumin, preoperative diagnosis of pancreatic cancer, concomitant pancreatitis, pancreatic thickness, operation time, intraoperative blood loss and stump closure technique.

Surgical procedures. All patients underwent laparotomy *via* midline or left subcostal incision. After assessment of resectability by exclusion of liver and peritoneal metastases, DP was performed. All patients underwent regional lymphadenectomy which included splenectomy. The stump closure technique was based on the discretion of the attending surgeon.

Hand-sewn stump closure: Pancreatic parenchyma was divided by a scalpel at the transection line, which was usually on the portal vein. Ligation of the main pancreatic duct was mandatory. If possible, the stump was closed by fish-mouth suturing using a single layer of non-absorbable interrupted sutures (3-0 or 4-0 prolene). In some patients with pancreatic cancer, because the transection line was located on the right side of the portal vein and superior mesenteric vein for complete tumor resection with macroscopically clear surgical margins, fish-mouth stump closure was not possible. Stump closure with stapler: Pancreatic parenchyma was clamped by intestinal forceps for 10 to 15 min to reduce the thickness of pancreatic parenchyma. Next, the stapler was gradually closed over a 5-min period. In all procedures described above, the peritoneum covering the pancreatic surface was kept intact. Then, a stapler was used for closure of the stump (Figure 1). Along with the advancement of stapling devices, three kinds of the stapler were included and evaluated in total in this retrospective study: three-line, six-line, six-line reinforced (Figure 2). One closed drain was placed

in the left subphrenic space through the foramen of Winslow close to the pancreatic stump.

Postoperative management. All patients received prophylactic antibiotics intraoperatively and for two days postoperatively. A nasogastric tube was used for decompression in all patients and was removed on postoperative day one if the discharge was below 200 ml. Oral food intake was started after nasogastric tube removal, beginning with water, and progressed over five phases, every 1-2 days, to reach a solid diet. Tight serum glucose control was postoperatively maintained by sliding-scale insulin therapy. Abdominal drain was removed on postoperative day 5 after confirmation of the absence of pancreatic fistula or infection. In patients with insufficient oral intake due to complications, including delayed gastric emptying (DGE) and insufficient solid oral intake in the absence of DGE, nutritional support was provided, predominantly *via* total parenteral nutrition.

Definition of outcome measures. POPF was defined according to the definitions proposed by the International Study Group on Pancreatic Fistula (13). Specifically, concentration of amylase in the drain fluid obtained on or after postoperative day 3 that was greater than three times the upper range of serum amylase concentration was diagnosed as POPF. POPFs were classified as grade A, B, or C according to their severity. In this study, the Clavien–Dindo classification was used for detailed evaluation of the severity of POPF (12). DGE was graded based on the International Study Group of Pancreatic Surgery (ISGPS) consensus definition (14). Mortality in the present study was in-hospital mortality.

Statistical analysis. Results were presented as a mean±standard deviation (SD) or medians with range, based on the distribution of data. Continuous variables were compared between the study groups using the independent samples *t*-test for normally distributed data or the Mann–Whitney *U*-test for abnormally distributed data. Categorical data were compared with the chi-square test or Fisher's exact test as appropriate. The univariate analysis of risk factors for POPF formation with a moderate or severe clinical impact classified as Clavien–Dindo IIIa or above, was performed in relation to the following preoperative and perioperative variables using a logistic regression model: age, sex, diabetes mellitus, preoperative serum albumin, preoperative diagnosis of pancreatic cancer, concomitant pancreatitis, pancreatic thickness, operation time, intraoperative blood loss, and stump closure technique. Variables were also compared by multivariate analysis using a logistic regression model. Variables to be entered into the multivariate analysis were chosen on the basis of the results of univariate analyses and consistency of the results of previous studies. All *p*-values were two-sided, and *p*<0.05 were considered significant. All analyses were performed using Stata® software (version 12.0; Stata, College Station, TX, USA).

Results

Incidence of POPF. The timing of POPF diagnosis did not differ between the two groups. Nineteen (79%) patients in group H did not develop POPF of any severity, whereas only nine (45%) patients in group S did not develop POPF (*p*=0.02). The incidence of POPF classified as Clavien–Dindo IIIa or above that required drainage was higher in

Figure 1. Stapler closure of the pancreatic stump. 1) Compression by intestinal forceps for 10-15 min. 2) Gradual clamping by a stapler for 5 min. 3) Division of the pancreatic parenchyma by a scalpel or cutter built in the stapler a few minutes after clamping by a stapler. 4) Stapled stump of the pancreas.

Figure 2. Improvements of stapling device. 1) Three-lined stapler. 2) Six-lined stapler. 3) Six-lined reinforced stapler.

group S than in group H (35% and 8%, respectively; $p=0.03$) (Table II). Overall incidence rates for POPF of any grade were 21% and 55% in groups H and S, respectively.

Perioperative outcomes. The median operation time and blood loss in groups H and S were 396 (range=228-558) min and 374 (range=255-544) min and 743±545 ml and 668±104 ml, respectively ($p=0.39$ and 0.63, respectively).

Postoperative pseudocyst formation was observed in 21% and 25% of the patients in groups H and S, respectively. There were no differences between the two groups in the incidence of other postoperative complications such as DGE, pseudoaneurysm formation, and surgical site infection. The rate of readmission, mainly for treatment of symptomatic pseudocysts, did not differ between the two groups. One patient with a pseudoaneurysm in group H was successfully treated by radiological intervention. The median duration of postoperative hospital stay was 14 (7-49) and 18 (8-77) days in groups H and S, respectively ($p=0.09$). Mortality rate was 0% in both groups.

Risk factors associated with high-grade POPF formation. Among a total of 44 patients retrospectively evaluated in the present study, the incidence rates of POPF according to the Clavien–Dindo classification were as follows: Clavien–Dindo 0–I, $n=19$; Clavien–Dindo II, $n=7$; Clavien–Dindo IIIa–IIIb, $n=9$. To identify risk factors associated with POPF, patients that developed POPFs with no clinical impact (Clavien–Dindo 0 or I, $n=19$) were compared with those that developed POPFs with a moderate or severe clinical impact (Clavien–Dindo IIIa or IIIb, $n=9$). Results of the univariate analysis and multivariate analysis of preoperative and perioperative factors using the logistic regression model are shown in Table III. No differences in pre-operative factors such as sex, age, primary indication for DP, and concomitant pancreatitis were observed between the two groups. In univariate analysis and multivariate analysis, the stump closure technique was identified as the only factor that was significantly associated with a higher incidence of POPF with clinical importance.

Discussion

POPF is a major complication of DP, leading to critical outcomes such as rupture of the pseudoaneurysm. The incidence of POPF in recent studies was reported as approximately 30%-60% (2-7). While numerous studies have been conducted to clarify the risk factors for POPF after DP, and also determine the optimal approach for pancreatic stump closure in DP to prevent POPF, ideal techniques remain a topic of intense debate and remain controversial.

The two most common techniques are scalpel resection followed by hand-sewn closure of the pancreatic remnant

Table II. Operative and postoperative clinical data.

	Group H (N=24)	Group S (N=20)	p-Value
Operative time (min)	396 (228-558)	374 (255-544)	0.39
Blood loss (ml)	743±545	668±104	0.63
Postoperative hospital stay (days)	14 (7-49)	18 (8-77)	0.09
Mortality	0	0	1
Date of diagnosis of POPF (postoperative days)	10.5±2.3	7.5±5.2	0.10
POPF (n, %)			
No	19, 79	9, 45	0.02
Clavien-dindo II	3, 12.5	4, 20.0	0.50
Clavien-dindo IIIa	2, 8.0	6, 30.0	0.06
Clavien-dindo IIIb	0	1, 5.0	0.27
POPF (rated as Clavien IIIa and more) (n, %)	2, 8.0	7, 35.0	0.03
Other postoperative complications			0.41
Delayed gastric emptying	2	0	
Pleural effusion	0	1	
Pseudoaneurysm	1	0	
Surgical site infection	2	1	
Paralytic ileus	0	1	
Pseudocyst at stump (n, %)	5, 21.0	5, 25.0	0.74
Readmission (n, %)	4, 17.0	2, 10.0	0.52

n, %, median [min-max], mean±standard deviation. POPF: Postoperative pancreatic fistula.

and stapler resection and closure (15). There are several comparative studies of hand-sewn and stapler closure.

In 2005, a meta-analysis which included two randomized clinical trials and eight observational studies reported a trend of lower POPF incidence with stapler use for stump closure compared with the hand-sewn closure: The odds ratio (OR) of POPF in the stapler group was 0.66 (95% confidence interval [CI], 0.35-1.26; $p=0.21$) (7). In 2011, a prospective, randomized, multicenter study (DISPACT trial) by Diener and colleagues reported that the incidence of POPF in DP was 32% among 177 patients with the stapler technique and 28% among 175 patients with the hand-sewn closure (OR, 0.84; 95%CI, 0.53-1.33; $p=0.56$) (16). The latest meta-analysis conducted by Zhang in 2015 reported the superiority of the stapler closure for POPF (17). However, they pointed out the existence of a publication bias in their analysis. Most observational studies comparing stapler and suture closure failed to show any significant difference in the incidence of POPF.

In the present study, we found that the hand-sewn closure was superior to the stapler closure, though the rate of POPF in the stapler closure group at our institute was higher than the recently reported incidence of POPF (19.7% to 35.5%) (15, 18, 19). The incidence of POPF with hand-sewn in the present

Table III. Risk factors with high-grade postoperative pancreatic fistula (Univariate analyses and multivariate analysis).

Variables	Clavien-Dindo 0 or I (N=28)	Clavien-Dindo IIIa or IIIb (N=9)	Univariate <i>p</i> -Value	Multivariate		
				OR	95% CI	<i>p</i> -Value
Age (years) (range)	64.5 (27-81)	64 (43-75)	0.89			
Gender (Male/Female)	20/8	6/3	0.79			
Diabetes mellitus	12 42.9	5 55.6	0.51	1.18	0.22-6.32	0.84
Serum albumin (g/dl)	4.1±0.5	4.0±0.2	0.54			
Pancreatic cancer	17, 60.7	5, 55.6	0.78			
Concomitant pancreatitis	6 21.3	3 33.3	0.47	1.41	0.23-8.73	0.71
Pancreatic thickness on the transection line (mm)	12.5±5.2	12.5±2.6	0.99			
Operative time (min)	387 (255-558)	368 (228-508)	0.59			
Blood loss (ml)	680±555	627±304	0.79			
Stump closure techniques (Hand-sewn/Stapler)	19/9	2/7	0.02	6.95	1.17-41.3	0.03

Display: n, %, median [min-max], means±standard deviation. OR: odds ratio, CI: confidence interval.

study was 21%, while the resent reported incidence of POPF in the hand-sewn ranges from 20 to 44% (15, 18, 20).

One major reason for the lower POPF rate with hand-sewn closure than with stapler closure might be the obligatory ligation of the main pancreatic duct, which is considered the most critical component of this technique. Bilimore reported that the incidence rates of POPF were 9.6% in patients with sutured closure of the pancreatic duct and 34% in patients who did not receive sutured closure. Multivariate analysis showed that failure to ligate the main pancreatic duct at the stump was a significant risk factor for pancreatic leakage with an OR of 5.0 (95%CI=2.0-10.0; $p=0.001$) (21). Kleeff and colleagues reported higher morbidity rate after stapler closure, raising the theory that stapling causes focal necrotizing pancreatitis (22). Similarly to the present study, Reeh and colleagues reported significantly higher POPF rate after stapler closure in their 283 consecutive DP cases (23). Sheehan and colleagues observed 14% POPF in the suture group compared to 25% in the stapler group (24). Some comprehensive studies found suture closure and stapler closure to be identical in terms of complications (4, 16, 20).

We also analyzed the risk factors for high-grade POPF after DP.

The risk factors for POPF after DP, which have been reported in previous studies, are divided into two categories: patients-related factors and surgery-related factors. The patients-related factors are as follows: male gender (5), advanced age (25, 26), a high American Society of Anesthesiologists score (3), smoking (4), an elevated body mass index ($>25 \text{ kg/m}^2$) (5, 27), decreased albumin levels (3), diabetes (28), primary pancreatic malignancy (29), soft pancreas parenchyma (20, 27), and chronic pancreatitis (30). In addition to transection methods and prophylactic

procedures, the surgery-related factors for POPF, which have been reported as independent predictors, are as follows: a prolonged operation time ($>240 \text{ min}$) (3, 22), intraoperative blood loss ($>1,000 \text{ ml}$) (3, 27), spleen preservation (20), the non-performance of ligation of the main pancreatic duct (21), transection at the tail (31), a greater volume of remnant pancreas (32), and multi-visceral resection (5). The risk factors for POPF after DP with stapler closure, which have been reported in previous studies (18, 25, 26, 28, 33, 34), were thickness of the pancreatic parenchyma and selecting appropriate stapling cartridge for the thickness of the pancreas. In our multivariate analysis using the ten risk factors mentioned above, only stump closure technique by stapler was the independent risk factor of high-grade POPF.

In consideration of the result of the present multivariate analysis, thickness of the pancreatic parenchyma should be considered in future evaluation of the stapling technique. Kawai and colleagues reported that pancreatic parenchymal thickness over 12 mm was associated with significantly increased incidence of POPF after DP using the stapler closure (18). The cut-off values in other studies were 27 mm and 16 mm (15, 26). In the current study, the averages of pancreatic thickness on the transection line were around 12.5 mm both in the patients' group with high-grade POPF and low-grade POPF. According to the thickness of the pancreas, the selection of a stapling device or the case selection for stapler use may improve the outcomes of stapler closure in DP.

Thus, the method of pancreatic stump closure (Hand-sewn or stapler) should be chosen with consideration of several factors such as pancreatic texture and thickness.

The present study was limited by its retrospective design and a small cohort that included three different stapler types in group S. Additionally, as this was a non-randomized study,

selection bias could not be ruled out. However, stapler closure is not a definitive method for pancreatic stump, and further improvement of this approach is needed.

There have been recent improvements in surgical staplers including the utilization of staple line reinforcement, with notable reductions in the incidence rates of POPF.

One study showed that POPF incidence was significantly reduced from 22% in 40 historical cases that underwent pancreatic stump closure with non-reinforcement stapler to 3.5% in 40 cases that underwent pancreatic stump closure with reinforcement-attached stapler ($p<0.05$), although the study was a single-center, retrospective study (35). Another prospective, single-center clinical trial reported that the incidence rates of ISGPS grade B/C POPF were 1.9% and 20% in reinforcement-attached and non-reinforced stapler groups, respectively ($p<0.01$) (36). However, the body mass index, which has been reported as a risk factor for POPF in other series (8, 11, 13, 14), was significantly higher in the no reinforcement group than in the mesh reinforcement group in this RCT. In addition, other reports showed a significantly increased incidence of POPF in reinforcement groups (15, 28). Confirmation of these results in patients receiving bioabsorbable mesh reinforcement in prospective, multi-center randomized clinical trials is necessary.

Based on the findings of the present as well as previous reports, along with the low incidence rates of Clavien IIIa–IIIb POPF (<8%) with hand-sewn closure, we suggest that hand-sewn closure should be considered for pancreatic stump closure due to its safety and cost-effectiveness.

Conclusion

Normal stapler use yielded higher rates of Clavien IIIa–IIIb POPF than hand-sewn closure of the pancreatic stump. In cases where stapler use is considered, pancreatic consistency and thickness, device and cartridge type, use of reinforcement, and pancreatic duct ligation should be incorporated into the surgical decision-making to more effectively control POPF rates. However, further investigation is needed to decrease POPF incidence.

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