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ORIGINAL ARTICLE – PANCREATIC TUMORS

A Multicenter, Randomized, Controlled Trial Comparing Reinforced Staplers with Bare Staplers During Distal Pancreatectomy (HiSCO-07 Trial)

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ABSTRACT

Background. Although distal pancreatectomy (DP) using a reinforced stapler is expected to reduce PF, no multicenter RCT has been performed. To investigate whether reinforced staplers reduce the incidence of clinically relevant pancreatic fistula (PF) after DP compared with staplers without reinforcement.

Methods. Between July 2016 and December 2017, patients scheduled for DP were enrolled in a multicenter, randomized, controlled trial (RCT) at nine hospitals in Hiroshima Japan. Patients were randomized either to reinforced stapler or bare stapler. The primary endpoint was incidence of clinically relevant PF. This RCT was registered with UMIN Clinical Trial Registry (UMIN000022341).

Results. A total of 122 patients were assigned to reinforced stapler ($n = 61$) or bare stapler ($n = 61$), and 119 patients (61 reinforced stapler and 59 bare stapler) were analyzed. There was no significant difference in the incidence of clinically relevant PF between the reinforced stapler and bare stapler groups (16.3% vs. 27.1%, $p = 0.15$). Furthermore, the rates of major complication (16.3% vs. 18.6%, $p = 0.74$), postpancreatectomy hemorrhage (0% vs. 3.4%, $p = 0.08$), and median postoperative in-hospital days (19 days vs. 20 days, $p = 0.78$) did not differ between the two groups. Within a subset of 82 patients in whom the thickness of pancreatic transection line was less than 14 mm, a significant difference was found in the incidence of clinically relevant PF (4.5% vs. 21.0% in the reinforced stapler vs. bare stapler groups, respectively, $p = 0.01$).

Conclusions. Reinforced stapler for pancreatic transection during DP does not reduce the incidence of clinically relevant PF compared to stapler without reinforcement.

The incidence of pancreatic fistula (PF) after distal pancreatectomy (DP) remains high at 10–30%.[1–4] To reduce the incidence of PF, several new techniques and equipment for pancreatic transection or stump treatment during DP have been developed.[5–7] For example, the use of a stapler is one of the most common techniques for pancreatic transection during DP. Staplers are easy to use and minimize technical differences among surgeons. However,

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the multicenter, randomized DISPACT trial found that stapler closure did not significantly reduce the incidence of PF after DP compared with handsewn closure.[8]

Recently, staplers were introduced that reinforce the resection line with various materials. These reinforced staplers are frequently used for pancreatic transection during DP. Several prior studies demonstrated that reinforced staplers reduced the incidence of PF after DP.[9–11] Notably, a randomized, controlled trial (RCT) found that reinforced staplers significantly reduced the incidence of clinically relevant PF.[12] This RCT was performed at a single institution with 100 enrolled patients, including 54 assigned to reinforced staplers, and the rate of clinically relevant PF with the use of a reinforced stapler was only 1.9%. In contrast, a multicenter, single-arm, prospective study from Japan found no improvement in the rate of clinically relevant PF with reinforced staplers, with an incidence of 12.4%.[13] Moreover, a meta-analysis concluded that there was no significant difference in the overall relative risk of developing a PF with the use of a reinforced stapler versus a stapler without reinforcement.[14] Thus, the efficacy of reinforced staplers for DP remains controversial. Based on these findings, the current multicenter, single-blind, randomized trial was conducted to investigate whether reinforced staplers reduce the incidence of clinically relevant PF after DP compared with staplers without reinforcement.

PATIENTS AND METHODS

Study Design

The current study was a multicenter, single-blind, randomized, parallel-group trial comparing the incidence of clinically relevant PF between reinforced reload with tri-staple and tri-staple without reinforcement during DP. The study was undertaken at nine hospitals in Hiroshima Japan. This RCT was conducted in compliance with the ethical principles of the Declaration of Helsinki, and the protocol was approved by the institutional review board at each participating institution. All patients provided written, informed consent before enrollment in the study. The study was registered in the University Medical Information Network-Clinical Trial Registry (UMIN-CTR), identification number 000022341.

Participants

Patients eligible for the study were required to meet the all of the following criteria: (1) undergoing DP with or without splenectomy; DP with celiac axis resection and/or other organ resections, (2) age 20 years or older; (3) Eastern Cooperative Oncology Group performance status of 0–1; and (4) adequate hematological, hepatic, and renal function (hemoglobin $\geq$ 9.0 g/dL, platelets $\geq$ 100,000/mm^3, total bilirubin $\leq$ 2.0 mg/dL, and serum creatinine $\leq$ 2.0 mg/dL).

Patients were excluded from participating if they met the following exclusion criteria: (1) severe heart failure (Class III or IV according to New York Heart Association functional classification); (2) severe liver failure (Grade C liver damage); (3) pulmonary disease required continuous oxygenation; (4) active malignant disease; or (5) complicating psychiatric disorder.

Protocol Treatment

Patients assigned to the reinforced stapler group underwent DP using the Endo GIA tri-staple (Covidien, Tokyo, Japan) with reinforcing sheet for pancreatic transection, whereas those assigned to the bare stapler group underwent DP using the Endo GIA tri-staple without reinforcement. The reinforcement material, Neoveil® (GUNZE, Kyoto, Japan), is polyglycolic acid, which is a bioabsorbable recombinant membrane made of a synthetic polymer. The pancreatic transection line was preoperatively identified after determining the surgical margins with multidetector computed tomography. The final determination was made by individual surgeons using intraoperative findings including intraoperative ultrasound and frozen section examination. The thickness of the pancreatic transection line was measured using preoperative computed tomography images based on the distance from the left portal vein edge, which was measured intraoperatively.

In both treatment groups, the pancreatic parenchyma was slowly compressed and fired over 5 min or more, and the condition of the pancreatic transection, including the presence of parenchymal damage or staple line hemorrhage, was evaluated and repaired if necessary. Both groups had two options for staple size, including a post-fire staple height of 3.0–4.0 mm (purple cartridge) or 4.0–5.0 mm (black cartridge). Surgeons determined staple size intraoperatively depending on the thickness of the pancreatic transection line.

Postoperatively, at least one drain was placed near the stump of the remnant pancreas, and amylase levels in the drainage fluid were measured on postoperative day (POD) 1, 3, and 5 in all patients. Drains were removed if the amylase level on POD 5 was less than three times the upper limit institutional normal serum value. When the amylase level on POD 5 was higher than three times the upper limit of serum normal value, subsequent drain management was left to the discretion of the attending surgeon. All patients received prophylactic antibiotics until POD 2 or less. Use of a somatostatin analog to prevent PF was prohibited.

Randomization

After providing written, informed consent, all required sections of a case report form were sent via fax to the HiSCO (Hiroshima Surgical study group of Clinical Oncology) data center. Patients were randomly assigned to reinforced stapler or bare stapler for pancreatic transection (allocation ratio 1:1) using a computer-generated modified minimisation in a central registry. Randomization was stratified by instutution, laparoscopic or open approach, and presence or absence of neoadjuvant therapy including chemo- and chemoradiotherapy. Patients were blinded to their group assignment, whereas investigators were aware of each patient's allocated treatment.

Outcomes

The primary endpoint was the incidence of clinically relevant PF (Grade B or C) as defined by the International Study Group of Pancreatic Fistula criteria.[15,16] Secondary endpoints included the incidence of major postoperative complication (Grade III or more based on the Clavien–Dindo classification system), postpancreatectomy hemorrhage as defined by the International Study Group of Pancreatic Surgery, incidence of clinically relevant PF stratified by thickness of the pancreatic transection line, postoperative in-hospital days, and mortality within 30 days of the operation.[17,18]

Statistical Analysis

The sample size for the current study was determined based on the primary endpoint. According to previous reports, the incidence of clinically relevant PF after DP with pancreatic transection using a stapler without reinforcement ranges from 16.4 to 28.3%.[5,6,8,12] On the other hand, the rate of clinically relevant PF with transection using a reinforced stapler is reported to range from 1.9 to 10%.[11,12,19] Based on these prior data, an assumed rate of clinically relevant PF in the reinforced stapler and bare stapler groups was estimated as 5% and 25%, respectively. To detect such a difference, 110 patients (55 in each group) would be required, which was calculated at a power of 80% with a significance level of 0.05 (two-sided). Estimating a 10% intraoperative withdrawal rate or exclusion after randomization, a total of 120 patients (60 in each group) were needed to meet the primary endpoint of the study. All analyses were performed using an intention-to-treat approach, in which all randomized patients were analyzed except those who did not undergo DP due to distant metastasis.

Patient characteristics, intraoperative findings, and postoperative complications were compared between the two groups using the χ^2 test or Fisher's exact test for categorical variables and the Wilcoxon two-sample test for continuous variables. With regard to the incidence of clinically relevant PF stratified by pancreatic thickness, one of the secondary endpoints, the optimal thickness cutoff value for predicting clinically relevant PF was determined by creating receiver operating characteristic curves. The incidence of clinically relevant PF was compared between reinforced stapler and bare stapler in subgroups stratified by the determined cutoff value. All statistical analyses were carried out using JMP statistical software version 13 (SAS Institute, Cary, NC). A p value < 0.05 was considered statistically significant.

RESULTS

Patient Enrollment

Between July 2015 and December 2017, 155 patients were scheduled to undergo DP and were assessed for eligibility. Of these, 122 patients were registered for the study, and randomly assigned to the reinforced stapler ($n = 61$) or bare stapler ($n = 61$) groups. The remaining 33 patients were not enrolled based on inclusion or exclusion criteria. After randomization, two patients in the stapler group were excluded, because they did not undergo DP due to peritoneal dissemination. In total, 119 patients, including 61 in the reinforced stapler group and 59 in the stapler group, were included in the intention-to-treat analysis (full analysis set). A consort diagram of the current study is shown in Fig. 1.

Patient Characteristics

A comparison of patient characteristics and preoperative status between the reinforced stapler and bare stapler groups is shown in Table 1. The two treatment groups were well-balanced for patient demographic data, including comorbidities, primary disease, preoperative adjuvant therapy, and preoperative laboratory data. A comparison of intraoperative findings between the two treatment groups is shown in Table 2. Notably, there were no significant differences in open versus laparoscopic approach, operative time, estimated blood loss, thickness of the pancreatic transection line, or types of stapler cartridge. In one patient in the stapler group, the staple transection could not be performed due to hard pancreatic parenchyma. The patient was included in all subsequent analyses based on the intention-to-treat principle, with the exception of the comparison of stapler cartridges, staple line hemorrhage, and parenchymal damage at the staple line.

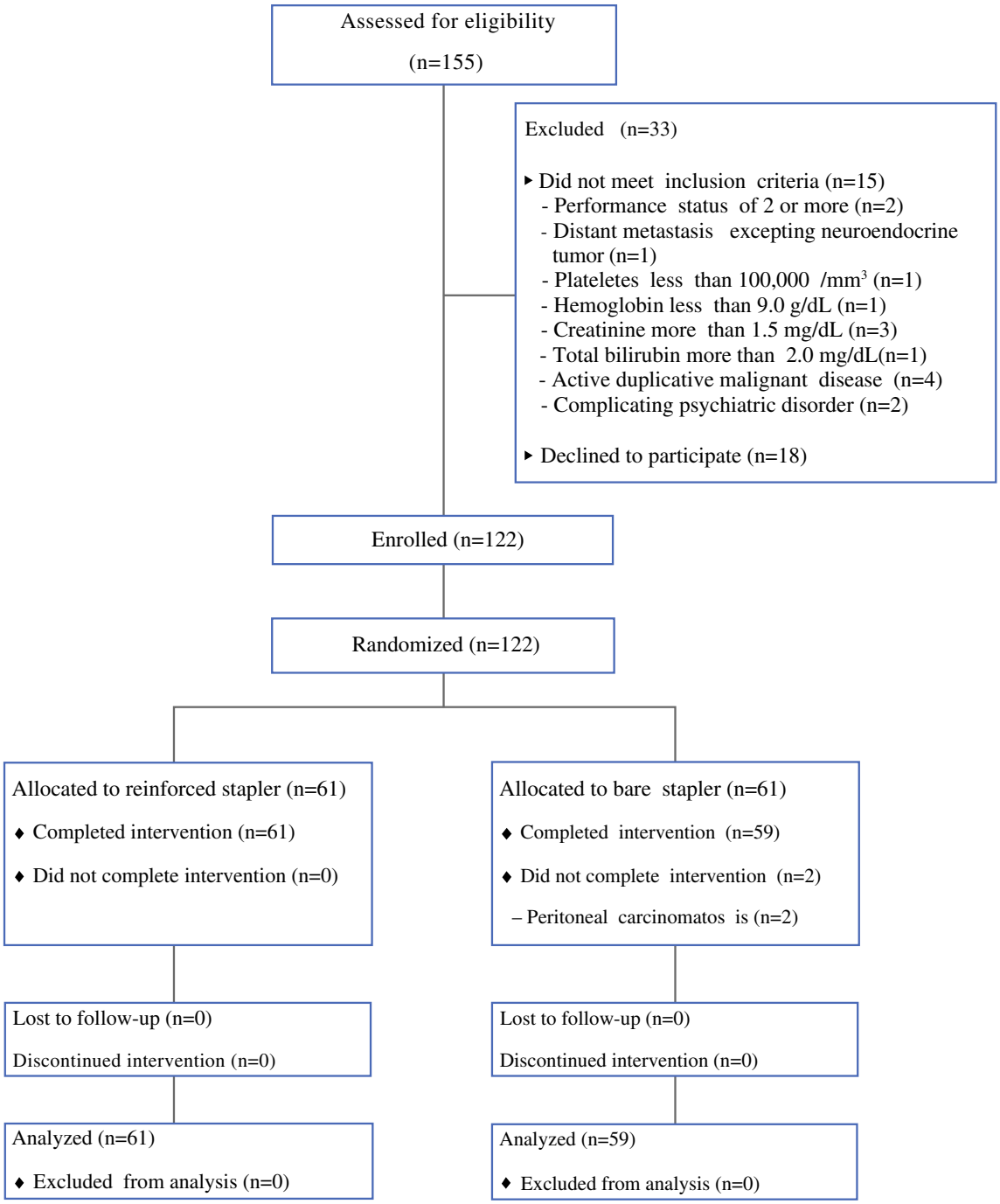


FIG. 1 Consort diagram for the trial

Primary and Secondary Endpoints

A comparison of postoperative outcomes between the two treatment groups is shown in Table 3. Of the 120 patients in the full analysis set, clinically relevant PF was observed in 26 (21.6%) patients, including 10 of 61 in the reinforced stapler group (16.3%) and 16 of 59 in the bare stapler group (27.1%). No significant difference in clinically relevant PF was found between the reinforced stapler and stapler groups ($p = 0.15$).

Regarding the secondary endpoints, there was no significant difference in the incidence of major complications (reinforced stapler 16.3% vs. bare stapler 18.6%, $p = 0.74$), postpancreatectomy hemorrhage (reinforced stapler 0% vs. bare stapler 3.4%, $p = 0.08$), or median number of postoperative in-hospital days (reinforced stapler 19 days vs. bare stapler 20 days, $p = 0.78$). No patient in either group

TABLE 1 Baseline characteristics of enrolled patients

Number (%) or median (IQR)	Reinforced stapler (n = 61)	Bare stapler (n = 59)	p Value
Age, years, median (IQR)	70 (62–76)	73 (67–78)	0.14
Gender (male/female)	31 (51)/30 (49)	25 (42)/34 (58)	0.35
Body mass index, median (IQR)	22.1 (19.9–25.0)	20.8 (19.6–23.9)	0.20
Performance status (0/1)	47 (77)/14 (23)	47 (80)/12 (20)	0.72
Diabetes mellitus (yes/no)	14 (23)/47 (77)	13 (22)/46 (78)	0.90
Oral treatment	10 (16)	10 (17)	0.93
Insulin use	4 (7)	3 (5)	0.73
Steroid use (yes/no)	1 (2)/60 (98)	3 (5)/56 (95)	0.28
Anticoagulant use (yes/no)	7 (11)/54 (89)	8 (14)/51 (86)	0.73
Preoperative adjuvant therapy (yes/no)	9 (15)/52 (85)	9 (15)/50 (85)	0.93
Pancreatic cancer/other disease (%)	28 (46)/33 (54)	35 (59)/24 (41)	0.14
Pancreatic cancer	28 (46)	35 (59)	
Intraductal papillary neoplasms	12 (20)	10 (17)	
Neuroendocrine tumor	9 (15)	6 (10)	
Mucinous cyst neoplasms	2 (3)	1 (2)	
Serious cyst neoplasms	1 (2)	1 (2)	
Solid pseudopapillary neoplasm	2 (3)	1 (2)	
Chronic pancreatitis	5 (8)	2 (3)	
Other disease	2 (3)	3 (5)	
Preoperative blood test, median (IQR)			
Leukocyte ($\times 10^3$/uL)	5.30 (4.65–6.68)	5.50 (4.54–6.30)	0.61
Hemoglobin (g/dL)	12.8 (11.4–13.9)	12.8 (11.6–13.8)	0.88
Platelet ($\times 10^3$/uL)	202 (140–259)	196 (122–245)	0.44
Total bilirubin (mg/dL)	0.6 (0.5–0.8)	0.6 (0.5–0.9)	0.27
Creatinine (mg/dL)	0.70 (0.64–0.92)	0.81 (0.68–0.93)	0.25
Albumin (mg/dL)	3.9 (3.7–4.3)	4.0 (3.8–4.3)	0.32
Amylase (IU/L)	76 (58–121)	77 (62–98)	0.65
C-reactive protein (mg/dL)	0.13 (0.03–0.53)	0.09 (0.03–0.20)	0.30
Hemoglobin A1c (%)	6.0 (5.6–6.7)	6.0 (5.7–6.4)	0.96

IQR interquartile range

suffered mortality within 30 days of the operation. The median thickness of the pancreatic transection line in patients with clinically relevant PF was 15.5 mm (interquartile range [IQR] 12.4–18.0), which was significantly larger than 11.8 mm (IQR 9.8–14.0) in patients without clinically relevant PF ($p < 0.001$; Fig. 2a). The receiver operating characteristics curve indicated that a thickness of 14 mm was the optimal cutoff value for predicting clinically relevant PF (Fig. 2b).

A comparison of the incidence of clinically relevant PF stratified by thickness of the pancreatic transection line is shown in Table 3. Within a subset of 82 patients with a pancreatic transection line thickness < 14 mm, the incidence of clinically relevant PF in the reinforced stapler group was significantly less than in the bare stapler group (reinforced stapler 4.5% vs. bare stapler 21.0%, $p = 0.01$). In contrast, no significant between-group difference was found in the 38 patients with a pancreatic transection line thickness ≥ 14 mm (reinforced stapler 47.0% vs. bare stapler 52.9%, $p = 0.57$).

DISCUSSION

The current multicenter, single-blind, randomized, parallel-group trial found that the use of a reinforced stapler for pancreatic transection during DP did not significantly reduce the incidence of clinically relevant PF compared with a stapler without reinforcement. The current RCT was conducted to determine the efficacy of reinforced staplers versus staplers without reinforcement during DP. This is the largest multicenter RCT comparing the incidence of clinically relevant PF after DP between reinforced staplers and staplers without reinforcement. Our study included several types of DP, such as laparoscopic approach, spleen

TABLE 2 Intraoperative findings

Number (%) or median (IQR)	Reinforced stapler (n = 61)	Bare stapler (n = 59)	p Value
Open/laparoscopic	47 (77)/14 (23)	45 (76)/14 (24)	0.91
Spleen preservation (yes/no)	2 (3)/59 (97)	5 (8)/54 (92)	0.21
Operative time (min)	275 (208–369)	223 (177–343)	0.17
Estimated blood loss (ml)	300 (118–466)	220 (76–463)	0.19
Dissection of SMA plexus (yes/no)	5 (8)/56 (92)	9 (15)/50 (85)	0.22
Portal vein resection (yes/no)	2 (3)/59 (97)	1 (2)/57 (98)	0.57
Celiac axis resection (yes/no)	8 (13)/59 (87)	4 (7)/57 (93)	0.24
Combined resection of other organs (yes/no)	5 (8)/56 (92)	4 (7)/55 (93)	0.76
Pancreatic texture (soft/hard)	56 (92)/5 (8)	55 (93)/4 (7)	0.76
Thickness at pancreatic transection line (mm)	12.0 (10.0–15.0)	12.5 (10.0–16.0)	0.46
Thickness of pancreatic transection line (</≥ 14 mm)			
< 14 mm	44 (72)	38 (64)	0.36
≥ 14 mm	17 (28)	21 (36)	
Completion of staple transection			
Completed	61 (100)	58 (98)	0.23
Not completed	0 (0)	1 (2)	
Type of stapler cartridges[a]			
Purple	31 (51)	30 (52)	0.92
Black	30 (49)	28 (48)	
Staple line hemorrhage (yes/no)[a]	5 (8)/56 (92)	7 (12)/51 (88)	0.48
Damage to parenchyma at stapling line (yes/no)[a]	5 (8)/56 (92)	3 (5)/55 (95)	0.50
Number of drains (1/2)	48 (79)/13 (21)	46 (78)/13 (22)	0.92

IQR interquartile range

[a]One patient in the stapler group was excluded because the staple transection could not be performed due to hard pancreatic parenchyma

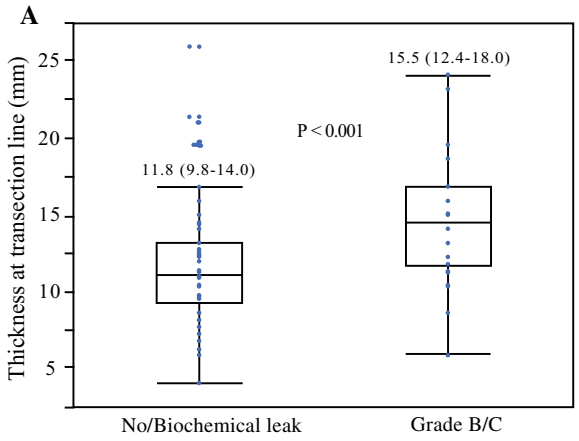
preservation, and extended DP. Moreover, the type of staple device was the same in both groups, except for the presence or absence of a reinforcement material. Therefore, we believe that the current RCT provides a standardized and versatile answer for the hypothesis that attachment of reinforced material on staple devices reduces the incidence of clinically relevant PF after DP compared with staplers without reinforcement.

The current study did not demonstrate any significant superiority of reinforced staplers in decreasing the incidence of clinically relevant PF rate after DP. It is possible that the sample size was too small to identify a difference, even though the sample size was statistically calculated. The estimated rate of clinically relevant PF in the reinforced stapler group was 5%, which was calculated based on the RCT reported by Hamilton et al.[12] However, the actual rate of clinically relevant PF in the current study was 16.3%, which was higher than our estimated rate. There are some differences between the prior single-center RCT and the current RCT that might account for this difference. First, the current RCT had no regulations regarding pancreatic parenchyma thickness, whereas the prior RCT excluded patients with excessive pancreatic thickness. Second, the type of stapler and reinforcing material used in the current study (Endo GIA tri-staple with Neoveil®) differed from the prior RCT (Echeron Stapler® with Seamguard® or Peristrips Dry®). Third, the current study included patients who underwent more extended DP, including celiac axis resection and other organ resection, which might increase the incidence of clinically relevant PF. These differences may underlie the differences in the rate of clinically relevant PF between the prior RCT and the current RCT. Indeed, the incidence of clinically relevant PF in the current study was similar to a prospective, single-arm, multicenter study from Kawai et al. This prospective study reported a 12.4% incidence of clinically relevant PF using the same reinforced stapler as the current study.[13] However, the study was not used for sample size estimation, because it was published after initiation of the current RCT. We believe that these factors resulted in a sample size that was too small to detect a significant reduction in clinically relevant PF using the reinforced stapler.

TABLE 3 Postoperative complications based on intention-to-treat analysis

Number (%) or median (IQR)	Reinforced stapler (n = 61)	Bare stapler (n = 59)	Odds ratio (95% CI)	p Value
Pancreatic fistula (all grade)	30 (49.1)	36 (61.2)	1.61 (0.78–3.33)	0.15
Biochemical leak	20 (32.7)	20 (33.9)		0.27
Grade B	10 (16.3)	16 (27.1)		
Grade C	0 (0)	0 (0)		
Clinically relevant pancreatic fistula	10 (16.3)	16 (27.1)	0.52 (0.21–1.28)	0.15
Clavien–Dindo classification (all grades)	31 (50.8)	29 (49.1)	0.93 (0.45–1.91)	0.85
I	4 (6.5)	0 (0)		0.13
II	17 (27.8)	18 (30.5)		
III	10 (16.3)	11 (18.6)		
IV	0 (0)	0 (0)		
Major complication (> Grade III)	10 (16.3)	11 (18.6)	1.16 (0.45–3.00)	0.74
Intra-abdominal abscess	6 (9.8)	8 (13.5)	1.43 (0.46–4.42)	0.52
Postoperative hemorrhage	0 (0)	2 (3.4)	N/A	0.08
Start of solid diet, median (days)	4 (3.5–5)	4 (3–5)		0.60
Delayed gastric emptying (all grades)	8 (13.1)	4 (6.7)	0.48 (0.13–1.69)	0.24
Grade A	2 (3.2)	0 (0)		0.17
Grade B	2 (3.2)	3 (5.1)		
Grade C	4 (6.5)	1 (1.7)		
Amylase in drainage fluid				
POD 1, (IU/L)	2154 (784–4442)	2310(906–5053)		0.65
POD 3, (IU/L)	274 (104–1071)	380 (130–1241)		0.48
POD 5, (IU/L)	163 (51–508)	389 (46–1073)		0.15
C-reactive protein level				
POD 1, (IU/L)	0.13 (0.03–0.53)	0.09 (0.03–0.20)		0.37
POD 3, (IU/L)	16.1 (9.4–21.6)	17.5 (13.4–21.2)		0.42
POD 5, (IU/L)	6.6 (3.8– 10.3)	7.9 (5.7–12.2)		0.13
Serum amylase level				
POD 1, (IU/L)	76 (58–121)	77 (62–98)		0.61
POD 3, (IU/L)	40 (29–58)	46 (31–68)		0.30
POD 5, (IU/L)	46 (31–59)	48 (30–77)		0.26
Time to drain removal, (days)	7 (5–21)	6 (5–21)		0.94
Percutaneous drainage	3 (4.9)	6 (10)	0.45 (0.10–1.91)	0.27
Wound infection	1 (1.6)	1 (1.7)	1.03 (0.06–16.9)	0.98
Ileus	2 (3.2)	2 (3.4)	1.03 (0.14–7.59)	0.97
Reoperation	2 (3.2)	1 (1.7)	1.96 (0.17–22.2)	0.57
Postoperative hospital stays, (days)	19 (14–30)	20 (13–28)		0.78
Readmission	1 (1.6)	3 (5.1)	3.21 (0.32–31.8)	0.28
30-day mortality	0 (0)	0 (0)	N/A	0.99
Comparison of clinically relevant pancreatic fistula stratified by thickness of pancreatic transection line				
Thickness of pancreatic transection line < 14 mm (n = 82)				
Clinically relevant pancreatic fistula (yes)	2 (4.5)	8 (21.0)	0.17 (0.03–0.90)	0.01
Thickness of pancreatic transection line ≥ 14 mm (n = 38)				
Clinically relevant pancreatic fistula (yes)	8 (47.0)	9 (52.9)	1.44 (0.39–5.28)	0.57

IQR interquartile range, *CI* confidence interval, *POD* postoperative day, *N/A* not available



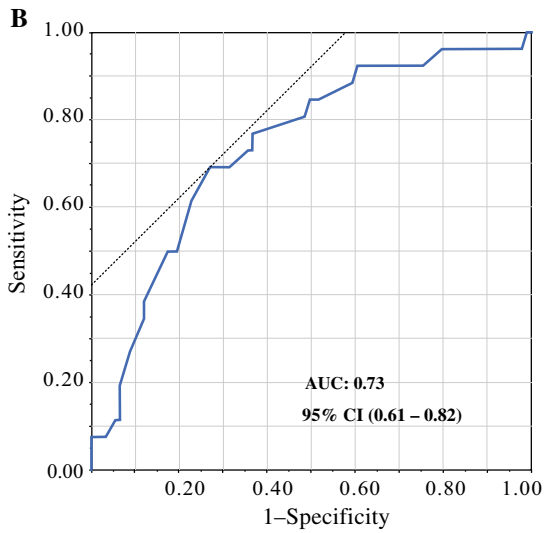


FIG. 2 Relationship between thickness of the pancreatic transection line and incidence of clinically relevant pancreatic fistula. **a** The median pancreatic transection line thickness in patients with and without clinically relevant PF was 15.5 mm (IQR 12.4–18.0) and 11.8 mm (IQR 9.8–14.0), respectively. Pancreatic transection line thickness in patients with clinically relevant PF was significantly higher than in patients without clinically relevant PF ($p < 0.001$). **b** The receiver operating characteristics curve indicated that a thickness of 14 mm was the optimal cutoff value for predicting clinically relevant PF. The area under the curve was 0.73 (95% confidence interval [CI] 0.61–0.82)

We found a significant reduction in the incidence of clinically relevant PF in the reinforced stapler group compared with the stapler without reinforcement group in the subgroup of patients with a pancreatic transection line thickness < 14 mm. One advantage of the reinforced stapler in DP is uniform compression of the pancreatic parenchyma. The reinforcement sheet may help seal the main and branch pancreatic ducts without injury. It is possible that this advantage is more pronounced in cases with thin pancreatic parenchyma. On the other hand, we found no significant difference in clinically relevant PF between the reinforced stapler and stapler groups in the subgroup of patients with a pancreatic transection line thickness ≥ 14 mm, with an incidence of more than 40% in both groups. The post-fire staple height reached a maximum of 5 mm in the stapler without reinforcement group; staple height was lower in the reinforced stapler group due to the thickness of the reinforced sheet. Pancreatic transection using a stapler for excessively thick pancreatic parenchyma may cause small pancreatic duct lacerations due to excess compression, resulting in a clinically relevant PF. Based on these results, pancreatic transection using a stapler may not be suitable when thick pancreatic parenchyma is encountered at the transection line, regardless of the presence or absence of reinforcement. Indeed, the current study demonstrated a significant correlation between pancreatic transection line thickness and incidence of clinically relevant PF. Several prior reports also suggested that thick pancreatic parenchyma is a risk factor for increased incidence of PF after DP.[20,21] Reanalysis of the current study after stratification by pancreatic thickness demonstrated that reinforced staplers may reduce the incidence of clinically relevant PF after DP in patients with thin pancreatic parenchyma at the transection line, whereas its efficacy was unclear in patients with thick pancreatic parenchyma.

This study has some inherent limitations due to its multi-institutional design. First, two staple heights could be selected intraoperatively according to the surgeon's discretion. Prior reports have suggested that inadequate staple height could influence the incidence of clinically relevant PF after DP.[22,23] Although the cartridge with higher staple height (black cartridge) was suggested for use with thick pancreatic parenchyma, it was difficult to set a clear-cut protocol for cartridge selection, because selection was based on several intraoperative findings. Second, drain management, including drain exchange, repositioning, and removal, was left to the attending surgeon's discretion when amylase levels in the drainage fluid on POD 5 were elevated. The time to drain removal in patients with high drain amylase levels could vary with the individual institution or attending surgeon, which could influence differences in biochemical leak and clinically relevant PF. Nevertheless, postoperative drainage fluid with high amylase levels must be carefully evaluated to prevent the development of life threatening complications. Therefore, a detailed protocol for drain management in cases of high amylase levels could not be established in the current study from an ethical standpoint.

CONCLUSIONS

The current study found no significant difference in the incidence of clinically relevant PF after DP using staplers with or without reinforcement. However, reinforced staplers might reduce clinically relevant PF after DP in patients with thin pancreatic parenchyma at the transection line.

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DISCLOSURE None of the authors has any commercial interests associated with this study.

ETHICAL APPROVAL This study was conducted in compliance with the ethical principles of the Declaration of Helsinki and the protocol was approved by the institutional review board at each participating institution. All patients provided written informed consent before enrollment in the study.

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