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ORIGINAL SCIENTIFIC REPORT

The Effect of Fibrinogen/Thrombin-Coated Collagen Patch (TachoSil®) Application in Pancreaticojejunostomy for Prevention of Pancreatic Fistula After Pancreaticoduodenectomy: A Randomized Clinical Trial

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Abstract

Background Fibrin sealants and topical glue have been studied to reduce the incidence of postoperative pancreatic fistulas (POPF) after pancreatico-enteric anastomosis, but a definitive innovation is still needed. We aim to evaluate the effectiveness of fibrin sealant patch applied to pancreatico-enteric anastomosis to reduce postoperative complications, including POPF.

Methods This study was a single-center, prospective, randomized, phase IV trial involving three pancreaticobiliary surgeons. The primary outcome was POPF; secondary outcomes included complications, drain removal days, hospital stay, readmission rate, and cost. Risk factors for POPF were identified by logistic regression analysis.

Results A total of 124 patients were enrolled. Biochemical leakage (BL) or POPF occurred in 16 patients (25.8%) in the intervention group and 23 patients (37.1%) in the control group (no statistical significance). Clinically relevant POPF occurred in 4 patients (6.5%) in both the intervention and control groups ($p = 1.000$). Hospital stay (11.6 days vs. 12.1 days, $p = 0.585$) and drain removal days (5.7 days vs. 5.3 days, $p = 0.281$) were not statistically different between two groups. Complication rates were not different between the two groups ($p = 0.506$); nor were readmission rates (12.9% vs. 11.3%, $p = 1.000$) or cost ($13,549 vs. $15,038, $p = 0.103$). In multivariable analysis, age and soft pancreas texture were independent risk factors for BL or POPF in this study. Applying fibrin sealant patch is not a negative risk factor, but the p value may indicate a likelihood of reducing the incidence of BL ($p = 0.084$).

Conclusions Fibrin sealant patches after pancreaticojejunostomy did not reduce the incidence of POPF or other postoperative complications. This study was registered at clinicaltrials.gov (NCT03269955).

Introduction

Pancreaticoduodenectomy (PD) is the standard surgical procedure for periampullary disease, and it is one of the most complex procedures in gastroenterological surgery. The rate of mortality is less than 4% according to the recent report, and it is reported to be about 1% in large volume centers (including our institution) through improvement of surgical techniques and postoperative management [1, 2]. However, morbidity of this procedure is still high, ranging from 30 to 40% [3, 4]. The complication rate of PD is higher than that of other operations, and this high morbidity is mainly attributable to the occurrence of

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postoperative pancreatic fistula (POPF) [5]. Pancreatico-enteric anastomosis is the most difficult step in PD, and POPF is caused by the procedure itself as well as other related factors, such as age, obesity, estimated blood loss, friability of pancreatic parenchyma, and size of pancreatic duct [6–9].

Since pancreatico-enteric anastomosis is developed, many materials have been proposed to reduce POPF [10, 11]. However, no innovative solution to definitively reduce the incidence of POPF has been invented. Although fibrin sealant patches were approved for targeted bleeding coverage, previous studies have shown additional beneficial results in sealing off air leaks of the trachea, thereby sealing off alveolar air leakage and reducing the incidence of lymphoceles after pelvic surgery, and decreasing cerebrospinal fluid leaks after neurosurgery [12–17]. In pancreatic surgery, methods using combined fibrin sealants and topical glue were also studied [18–20]. Mita et al. [18] reported in a retrospective single-arm study that 40 patients to whom fibrin sealants were applied showed a 20% reduction in the incidence of POPF compared with a previous study. Chirletti et al. [19] compared 27 patients using fibrin sealants and 27 control patients. There was no significant difference between the two groups, but the authors nevertheless reported the possibility of improving POPF with fibrin sealants. Recently, Schindl et al. [20] reported a randomized clinical trial on the effect of a fibrin sealant patch on pancreatic fistula formation after PD, and the results showed that use of a fibrin sealant patch did not reduce the occurrence of POPF and other complications.

Our institution has empirically used fibrin sealant patches on pancreatico-enteric anastomosis during PD, and we still question its utility. We believed that we could clearly determine the effects of fibrin sealant patches because pancreatico-enteric anastomosis is performed uniformly at our institution. Therefore, we planned a randomized clinical trial to investigate the efficacy of fibrin sealant patches for preventing POPF. We hypothesized that POPF rates would be lower in the fibrin sealant patch group. The purpose of this study was to evaluate the effectiveness of fibrin sealant patch application to pancreatico-enteric anastomosis to reduce postoperative complications, including POPF.

Materials and methods

We enrolled consecutive patients who underwent pancreaticoduodenectomy in the Division of Hepato-Biliary and Pancreatic Surgery, Department of Surgery at Asan Medical Center between February 2017 and May 2018. This study was designed as a single-center, prospective, randomized, parallel-group, phase IV, single-blind (participant) trial involving three pancreaticobiliary surgeons, each with annual frequency of more than 70 PD cases. The study protocol was approved by the institutional research review board, and written informed consent was obtained from each enrolled patient. This study was registered at clinicaltrials.gov (NCT03269955), was conducted in accordance with the Declaration of Helsinki, and was performed according to CONSORT guidelines [21].

Inclusion and exclusion criteria

Included in this study were patients who were scheduled for open PD with periampullary cancer or borderline tumor, without a history of chronic pancreatitis or distant metastasis. Age ranged from 19–80 years. ECOG performance score was 0–2. Blood cell count was at least 3000/mm^3, absolute neutrophil count at least 1500/mm^3, and platelet count was at least 125,000/mm^3. AST and ALT were less than 3 times upper limit of normal. Creatinine was no greater than 1.5 times upper limit of normal. These patients were excluded if there was an abnormality in these tests because there may be other diseases that could not be identified before surgery and the possibility of affecting patient recovery period and hospital cost. Patients had the ability to ask any questions to enhance understanding, and the willingness to sign a written informed consent document. Patients with distant metastases, recurred tumors, pregnancy, breastfeeding, active or uncontrolled infection, and uncontrolled heart disease were not eligible. Patients with moderate or severe comorbidities who were thought to be impacted in regard to quality of life or nutritional status (liver cirrhosis, chronic kidney failure, heart failure, and others) were also excluded. Patients who had undergone other major abdominal surgeries were also excluded.

Surgical technique

Resection methods during PD in our institution have been reported previously [22]. After resection in all cases, we performed pancreaticojejunostomy for pancreatico-enteric anastomosis. Pancreaticojejunostomy was carried out using the double-layered, end-to-side duct-to-mucosa method. First, we sutured the jejunum and posterior wall of the pancreas parenchyma with polypropylene suture 4-0. After that, we made a small hole in the mucosa with electrocautery. Suture of jejunal mucosa to the pancreas duct was performed with polydioxanone 5-0, with interrupted sutures. A polyethylene internal stent was inserted in the pancreatic duct of all patients, both intervention and control groups. Finally, sutures were placed between the jejunum and the anterior wall of the pancreas parenchyma with prolene 4-0. End-to-side choledochojejunostomy was

also performed. Antecolic duodenojejunostomy or gastrojejunostomy with jejunojejunostomy was performed. Two closed suction drains were placed at the superior and inferior borders of pancreaticojejunostomy site. All three surgeons used the same pancreaticojejunostomy method.

Intervention

In patients randomized to the intervention group, pancreaticojejunostomy was covered with a 9.5 cm × 4.8 cm fibrinogen/thrombin-coated collagen patch (TachoSil®; Takeda Austria, Linz, Austria) on the front and back aspects of the anastomosis site. After this, fibrin glue was applied to the pancreaticojejunostomy site in PD. Only fibrin glue alone was applied to the pancreaticojejunostomy site in the control group. Feature of intervention is shown in Fig. 1.

Outcome

Primary outcome measures

a. Incidence of pancreatic fistula

The evaluation of pancreatic fistula was based on the International Study Group of Pancreatic Fistula (ISGPF) [23]. According to their criteria, pancreatic fistula were evaluated by measuring the amylase level of the drain tube on postoperative day 3, and the pancreatic fistula was judged to be present when the amylase level was 3 times higher than the normal level of amylase in the blood.

b. Incidence of clinically relevant pancreatic fistula

The grade uses ISGPF grading, while grades B and C are clinically relevant pancreatic fistulas. According to ISGPF definition [23], maintenance drain for more than 3 weeks, clinically relevant change in management of POPF, intervention for POPF, and sign of infection without organ failure were defined as POPF grade B. POPF grade C was defined as reoperation, organ failure, or death related to POPF.

Secondary outcome measures

a. Incidence of complications

Complications other than pancreatitis included all complications after PD. Delayed gastric emptying and postoperative bleeding complied with the criteria of the International Study Group, and the severity of complications was classified through the Clavien–Dindo classification [24].

b. Drainage removal days

The timing of drain tube removal was determined based on the time of removal of the last drain tube. The removal of the drain tube was assessed at the discretion of the surgeon.

c. Death

Any patients who died during hospitalization were noted. One patient died within 90 days of discharge; this result included death.

d. Readmission rate

Readmission rates included all cases of readmission after discharge due to problems associated with PD. Readmissions not related to PD were not included.

e. Period of hospitalization after surgery

The duration of the hospital stay was calculated based on the time when the specific patient was discharged.

f. Cost

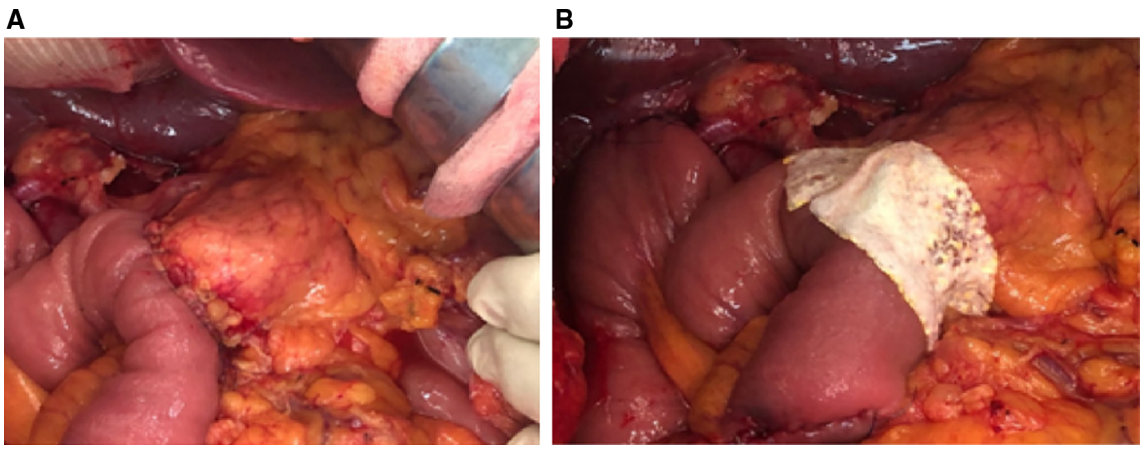

Fig. 1 Feature of intervention. **a** Pancreaticojejunostomy before applying fibrin sealant patch. **b** Pancreaticojejunostomy was covered with a 9.5 cm × 4.8 cm fibrin sealant patch on the front and back aspects of the anastomosis site

The assessment of costs was defined as the total cost of care from the time of admission for surgery until discharge. Fibrin sealant patch was priced at 349 dollars in South Korea. The cost of the fibrin sealant patch used in this study was not billed to the patient.

Sample size

We assumed that 20% of the patients undergoing PD with pancreaticojejunostomy would develop a biochemical leakage (BL) or POPF after surgery, based on previous studies [18, 22, 25]. Furthermore, a 15% reduction in BL or POPF was considered to be a significant clinical improvement using a fibrin sealant patch. Based on this hypothesis, a sample size of 112 patients, 56 in each group, was calculated based on type 1 error $\alpha = 0.05$ and power $(1 - \beta) = 0.8$, using a two-sided χ^2 test. Factoring in a dropout rate of 10%, we recruited a total of 126 patients, 63 per each group.

Randomization

We enrolled 63 patients in each group, and a total of 126 patients were randomized with block randomization before surgery. Block randomization was performed to correct the imbalance in the number of groups. A was assigned to the intervention group, and B was assigned to the control group; the groups were then determined as: (1) ABBA, (2) BBAA, (3) ABAB, (4) BABA, (5) AABB, and (6) BAAB. Patients were randomized by an independent researcher at Asan Medical Center. The blocks were selected based on the number on thrown dice.

Statistical analysis

Statistical analyses were performed using SPSS 21.0 (IBM Corp., Armonk, NY, USA). Continuous variables were compared using Student's *t* test. Categorical variables were compared with the Chi-square test, Fisher's exact test, or by linear association. The tests were two-sided, and p value ≤ 0.05 was considered significant. Risk factors for the occurrence of BL or POPF were tested in a multivariable logistic regression with background elimination model, with results expressed as odds ratios with 90% confidence intervals. The significance level for variable elimination was 0.05.

Results

Patient recruitment started from February 2017–May 2018, and follow-up ended in December 2018. In total, 126 patients who underwent PD were included in the study, with 62 patients in the intervention group and 64 patients in the control group (Fig. 2). Two patients in the control group who did not undergo PD were excluded from this study; one underwent total pancreatectomy due to positive resection margin on intraoperative consultation diagnosis from the remnant pancreas; the other underwent palliative bile duct resection. There was no follow-up of these

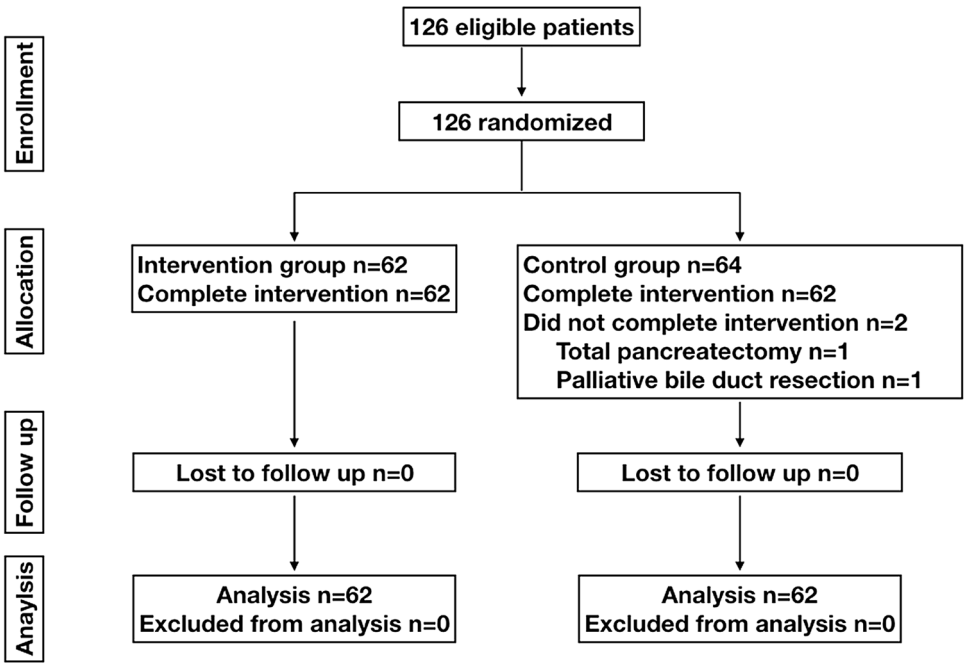

Fig. 2 CONSORT flow diagram for the trial

Table 1 Patient characteristics

Variables	Intervention ($N = 62$)	Control ($N = 62$)	p value
Age (years)			
Mean (±SD)	62.03 (±10.95)	63.16 (±9.02)	0.532
Sex, n (%)			
Male	42 (67.7)	37 (59.7)	0.455
Female	20 (32.3)	25 (40.3)	
BMI (kg/m^2)			
Mean (±SD)	23.69 (±3.65)	23.23 (±2.83)	0.434
Vein resection			
Yes	15 (24.2)	11 (17.7)	0.509
No	47 (75.8)	51 (82.3)	
Disease			
PDAC	31 (50)	33 (53.2)	0.857
Others	31 (50)	29 (46.8)	
Pancreatitis			
Yes	29 (46.8)	27 (43.5)	0.857
No	33 (53.2)	35 (56.5)	
Pancreas duct size (mm)			
1≤	2 (3.2)	2 (3.2)	0.887
2≤	12 (19.4)	11 (17.7)	
3≤	12 (19.4)	14 (22.6)	
4≤	9 (14.5)	11 (17.7)	
5≤	27 (43.5)	24 (38.7)	
Pancreas texture			
Soft	39 (62.9)	37 (59.7)	0.854
Firm	23 (37.1)	25 (40.3)	
Alternative Fistula Risk Score$^+$			
Low	19	19	1.000
Intermediate	37	38	
High	6	5	
Operation time (min)			
Mean (±SD)	275 (±59)	277 (±55)	0.856
Estimated blood loss (ml)			
≤400	59 (95.2)	57 (91.9)	0.543
401–700	1 (1.6)	1 (1.6)	
701–1000	1 (1.6)	2 (66.7)	
1001≤	1 (1.6)	2 (66.7)	
Neoadjuvant, n (%)			
Yes	7 (11.3)	7 (11.3)	1.000
No	55 (88.7)	55 (88.7)	

$^+$Alternative fistula risk score was determined according to the definition of Dutch Pancreatic Cancer Group [26]

SD standard deviation, *BMI* body mass index, *PDAC* pancreas ductal adenocarcinoma

patients. The study, therefore, evaluated a total of 124 patients, with 62 in the intervention group and 62 in the control group. Each of three surgeons operated 30, 36, and 58 patients. Age, sex, body mass index, concurrent vein resection, disease characteristics, pancreatitis, pancreas duct size, pancreas texture, alternative fistula risk score [26], operation time, estimated blood loss, and neoadjuvant chemotherapy were not statistically different between two groups (Table 1).

Primary outcomes

BL or POPF occurred in 16 patients (25.8%) in the intervention group and in 23 patients (37.1%) in the control

Table 2 Rates of POPF

Variables	Intervention (N = 62)	Control (N = 62)	p value
POPF[+], n (%)	16 (25.8%)	23 (37.1)	0.246
POPF grade, n (%)			
Biochemical leakage	12 (19.4)	19 (30.6)	0.323
B	4 (6.5)	3 (4.8)	
C	0 (0.0)	1 (1.6)	
Clinically relevant POPF, n (%)	4 (6.5)	4 (6.5)	1.000
Alternative fistula risk score* (Negative/biochemical leakage/clinically relevant POPF), n			
Low	18/1/0	19/0/0	0.317
Intermediate	25/11/1	18/18/2	0.088
High	3/0/3	2/1/2	0.771

[+]POPF was graded according to the definition updated in 2016 by International Study Group Pancreatic Fistula [23]

*Alternative fistula risk score was determined according to the definition of Dutch Pancreatic Cancer Group [26]

group (Table 2). Occurrence rates were different, but there was no statistically significant difference between the two groups. Clinically relevant POPF occurred in 4 patients (6.5%) in the intervention group, as well as in 4 patients in the control group (p = 1.000). According to the alternative fistula risk score grade, there was also no difference in the proportion of POPF between the low-, intermediate-, and high-risk patients between the two groups.

Secondary outcomes

There were no significant differences in postoperative outcomes (Table 3). Hospital stay (11.6 days vs. 12.1 days, p = 0.585) and drain removal days (5.7 days vs. 5.3 days, p = 0.281) were not different between the two groups. The complication rate was not different between the two groups (p = 0.506). By limiting to Clavien–Dindo class 3 or higher, there was no difference between the intervention and control groups (4.8% vs. 9.7%, p = 0.491). There was one mortality case in the control group. POPF grade C occurred in this patient, and the patient expired because of septic shock, with two reoperations at postoperative day 43. Of the total patients, reoperation occurred only in the case of the patient who died. The control group patient who underwent angioembolization due to superior mesenteric artery pseudoaneurysm with intensive care belonged to Clavien–Dindo grade 4. Readmission rate (12.9% vs. 11.3%, p = 1.000) and cost ($13,549 vs. $15,038, p = 0.103) were not different between the two groups.

Risk factors for POPF

A multivariable logistic regression model identified age (p = 0.028) and soft pancreas texture ($p < 0.001$) as independent risk factors for BL or POPF in the current study (Table 4). Applying fibrin sealant patch did not indicate a negative risk factor for BL or POPF, but the p value was 0.084.

Table 3 Postoperative outcome

Variables	Intervention (N = 62)	Control (N = 62)	p value
Hospital stay (days)			
Mean (±SD)	11.6 (±3.8)	12.1 (±6.6)	0.585
Drain removal (days)			
Mean (±SD)	5.7 (±2.4)	5.3 (±2.4)	0.281
Complications grade[+], n (%)			
No	32 (51.6)	30 (48.4)	0.506
Grade I	12 (19.4)	13 (21.0)	
Grade II	15 (24.2)	13 (21.0)	
Grade III	3 (4.8)	4 (6.5)	
Grade IV	0 (0.0)	1 (1.6)	
Grade V	0 (0..0)	1 (1.6)	
Mortality*			
Yes	0 (0.0)	1 (1.6)	1.000
No	62 (100)	61 (98.4)	
Readmission			
Yes	8 (12.9)	7 (11.3)	1.000
No	54 (87.1)	55 (88.7)	
Cost (dollars)			
Mean (±SD)	13,549 (±2820)	15,038 (±6515)	0.103

[+]Complications grade was classified according to the Clavien–Dindo classification [19]

*Mortality was patient who died during hospitalization. A patient died within 90 days of operation, this result also included to death

Discussion

Various studies are being performed to reduce POPF after pancreatectomy. These studies include anastomosis methods, stump closure methods, and various products used

Table 4 Univariate and multivariate models of risk factor for biochemical leakage or POPF

Variables	No (N = 85)	Biochemical leakage/ POPF (N = 39)	Univariate odds ratio	p value	Multivariate* odds ratio	90% CI		p value
						Lower	Upper	
Age (years)								
Mean (±SD)	61.24 (±10.36)	65.56 (±8.61)	1.049	0.028	1.061	1.1015	1.1110	0.028
Sex, n (%)								
Male	58 (68.2)	21 (53.8)	0.543	0.124	0.436	0.190	1.000	0.100
Female	27 (31.8)	18 (46.2)						
BMI (kg/m^2)								
Mean (±SD)	23.28 (±3.23)	23.86 (±3.33)	1.055	0.357				
Vein resection								
Yes	24 (28.2)	2 (5.1)	0.137	0.009				
No	61 (71.8)	37 (94.9)						
Disease								
PDAC	56 (65.9)	8 (20.5)	0.134	<0.001				
Others	29 (34.1)	31 (79.5)						
Pancreatitis								
Yes	45 (52.9)	11 (28.2)	0.349	0.012				
No	40 (47.1)	28 (71.8)						
Pancreas duct size (mm)								
Mean (±SD)	4.54 (±2.38)	3.74 (1.82)	0.829	0.07				
Pancreas texture								
Firm	47 (55.3)	1 (2.6)	0.021	<0.001	0.018	0.003	0.102	<0.001
Soft	38 (44.7)	38 (97.4)						
Intervention								
Intervention	46 (54.1)	16 (41.0)	0.59	0.178	0.426	0.189	0.960	0.084
control	39 (45.9)	23 (59.0)						
Operation time (min)								
Mean (±SD)	279 (±61)	269 (±47)	0.997	0.353				
Estimated blood loss (ml)								
≤400	79 (92.9)	37 (94.9)	1.405	0.686				
>400	6 (7.1)	2 (5.1)						
Neoadjuvant, n (%)								
Yes	12 (14.1)	2 (5.1)	0.329	0.159				
No	73 (85.9)	37 (94.9)						

*Multivariate logistic regression with backward elimination

after anastomosis. The mechanism of action of fibrin sealant patches is based on the interaction between active biological substances (human fibrinogen and human thrombin) and the physiology of fibrin clot formation. There were several studies on the use of fibrin sealant patches for preventing POPF after distal pancreatectomy [27–31]. Silvestri et al. [30] reported that use of fibrin sealant patches seems to be associated with a lower incidence of POPF grade C. Two previous multicenter, randomized controlled trials reported that fibrin sealant patches had no significant effect on the rate of POPF after distal pancreatectomy [28, 29]. For pancreaticojejunostomy, there were three studies on fibrin sealant patches. Two retrospective studies reported that fibrin sealant patches are feasible and safe with 7.4–20% POPF rates after PD with pancreaticojejunostomy [18, 19]. Schindl et al. [20] reported a multicenter, randomized clinical trial of the effect of a fibrin sealant patch after PD, and that study was the first randomized clinical trial on the fibrin sealant patch. In that study, rates of BL or POPF were 63% in the intervention group and 56% in the control group. Clinically relevant POPF rates were 23% in the intervention group

and 14% in the control group. The study reported that there was no POPF reduction with the use of fibrin sealant patches after PD, but they could not provide a conclusive explanation of the higher incidence of BL.

The results of our study are reliable when compared with previous reports. BL or POPF occurred in 39 patients (31.5%), and POPF B or C occurred in 8 patients (6.5%) of the patients enrolled in our current study. The acceptable incidence of BL and POPF could be explained by each surgeon's experience. All three surgeons participating in the study had experience in performing more than 400 PD cases, and performing more than 70 PD cases per year. All of the surgeons used the same pancreaticojejunostomy methods, and the occurrence rate of clinically relevant POPF was not different between the three surgeons (8.6% vs. 3.3% vs. 5.6%, $p = 0.537$). This eliminates the variability in the type of anastomosis method as a potential confounding variable and increases the internal validity of fibrin sealant efficacy. Berger et al. also described that the limitations in their dual institution comparative study were the institutional differences in surgical procedures and POPF rate [32].

Nevertheless, the current study has shown no statistically significant superiority of using fibrin sealant patches regarding incidence of BL or POPF after PD with pancreaticojejunostomy. Although there was no statistical difference, the incidence of BL was lower in the intervention group (19.4% vs. 30.6%), suggesting that the BL rate may vary if more patients are included. Additionally, in multivariable analysis of risk factors, the p value was 0.084 when the fibrin sealant patch was applied, but it was not completely meaningless because the number of patients in this study was not sufficient to perform the risk factor analysis.

There were no reductions in hospital stay, drain removal days, complications, readmission rates, and hospital expenses in patients with application of fibrin sealant patches. These results are probably because of the same incidence of clinically relevant POPF and grade 3 or higher complications between the two groups. These results were also found in another randomized clinical trial that studied fibrin sealant patches after pancreatectomy [20, 31]. The complication rate of the current study was also acceptable when compared with other studies [32, 33]. Berger et al. reported a randomized clinical trial of pancreaticojejunostomy after PD with 51.8% overall morbidity and 18.3% major complications [32]. Miyauchi et al. [33] reported 31.7% of Clavien–Dindo grade 3 of higher cases with complications after PD. In the current study, there were 62 cases (50%) of overall morbidity and 9 cases (7.3%) of grade 3 or higher complications after PD. Low incidence of major complications also can be explained by the accumulation of experience. Our institution reported a chronologic change of clinicopathologic feature after pancreatectomy for pancreatic ductal adenocarcinoma [34]. In the study, there is a statistical difference in complication rates between early periods and the last 7-year period.

The risk factors for BL or POPF were age and soft pancreas texture in our study. Age, vein resection, disease, pancreatitis, and pancreas texture were significant risk factors in univariate analysis, but age and pancreas texture were risk factors for POPF in multivariate analysis. Several studies reported that soft pancreas texture was associated with clinically relevant POPF [6, 35, 36]. Wang et al. [9] reported that POPF occurs more frequently in elderly patients, patients with cystic neoplasms, or patients with an episode of acute pancreatitis during pancreas enucleation. There was a randomized clinical trial that reported that use of polyglycolic acid mesh is associated with a significantly reduced rate of clinically relevant POPF after distal pancreatectomy [37], but to our knowledge, there was no study published on fibrin sealant patches as a negative risk factor to reduce BL or POPF. Although the incidences of clinical relevant POPF were 6.5% in both groups, the incidence of BL was not statistically significant, but there was a still difference in the current study. As we mentioned above, although applying fibrin sealant patch is not a negative risk factor, the p value may indicate a likelihood of reducing the incidence of BL. A p value of less than 0.1 may be interpreted as statistically significant when the number of enrolled patients is not sufficient. Therefore, our results suggest that studies including more number of patients are needed to clearly identify the efficacy of the fibrin sealant patch for preventing BL.

The first limitation of this study was the potential for it to be underpowered. As it was designed to be conducted at a single institution in a short period, and considering the recruitment capacity, it was designed to have 80% power. Risk factor interpretation was limited because the number of cases was not large. More clear conclusion about the effects of fibrin sealant patch is needed through multicenter randomized clinical trial involving a large number of patients. In addition, this study did not show the positive effects of the fibrin sealant, but if all studies reported only positive findings, future research and practice would be biased.

This study is also meaningful because the application of fibrin sealant suggested the possibility of reducing BL and experienced surgeons performed the same method of pancreaticojejunostomy with or without fibrin sealant patches, eliminating potential confounding variables, and yielding acceptable POPF and complication rates.

In summary, fibrin sealant patches after pancreaticojejunostomy did not reduce the incidence of POPF and postoperative complications in this randomized study.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests in relation to this study.

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