Review Article

Clinical trials to reduce pancreatic fistula after pancreatic surgery—review of randomized controlled trials

Yuji Kitahata, Manabu Kawai, Hiroki Yamaue

Second Department of Surgery, Wakayama Medical University, School of Medicine, Wakayama, Japan

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Correspondence to: Hiroki Yamaue, MD. Second Department of Surgery, Wakayama Medical University, School of Medicine, 811-1 Kimiidera, Wakayama 641-8510, Japan. Email: yamaue-h@wakayama-med.ac.jp.

Abstract: Pancreatic fistula is one of severe postoperative complications that occur after pancreatic surgery, such as pancreaticoduodenectomy (PD) and distal pancreatectomy (DP). Because pancreatic fistula is associated with a higher incidence of life-threatening complications. In order to evaluate procedure or postoperative management to reduce pancreatic fistula after pancreatic surgery, we summarized some randomized controlled trials (RCTs) regarding pancreaticoenterostomy during PD, pancreatic duct stent during PD, procedure to resect pancreatic parenchyma during DP, and somatostatin and somatostatin analogues after pancreatic surgery. At first, we reviewed nine RCTs to compare pancreaticogastrostomy (PG) with pancreaticojejunostomy (PJ) during PD. Next, we reviewed five RCTs, to evaluate the impact of pancreatic duct stent during PD. Regarding DP, we reviewed six RCTs to evaluate appropriate procedure to reduce pancreatic fistula after DP. Finally, we reviewed eight RCTs to evaluate the impact of somatostatin and somatostatin analogues after pancreatic surgery to reduce pancreatic fistula. The best way to prevent pancreatic fistula after pancreatic surgery remains still controversial. However, several RCTs clarify a useful procedure to reduce in reducing the incidence of pancreatic fistula after pancreatic surgery. Further RCTs to study innovative approaches remain a high priority for pancreatic surgeons to prevent pancreatic fistula after pancreatic surgery.

Keywords: Pancreatic surgery; clinical trial; pancreatic fistula

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Introduction

The morbidity rate after pancreatic surgery still remains high in the range of 15% to 65%, although mortality has decreased to less than 5% due to recent advances in surgical techniques and perioperative management (1-7). In particular, pancreatic fistula is one of the most severe postoperative complications after pancreatic surgery. Pancreatic fistula is reportedly associated with a higher incidence of life-threatening complications, such as intra-abdominal abscess, intra-abdominal hemorrhage, and sepsis (8-12). A strategy to decrease pancreatic fistula after pancreatic surgery is urgently required.

The various innovative techniques, including operative techniques, intensive care medicine and pharmacological agents have been utilized to prevent the incidence of pancreatic fistula after pancreatic surgery. This review summarizes the randomized controlled trials (RCTs) to prevent pancreatic fistula after pancreatic surgery.

Definition of pancreatic fistula

In 2005, an international study group of pancreatic surgeons (ISGPF) proposed a consensus definition and clinical grading of postoperative pancreatic fistula (13). Pancreatic fistula was defined by ISGPF guidelines as follows: amylase

level in drainage fluid on POD 3 that was more than 3 times the serum amylase level. Pancreatic fistula was classified into three categories by ISGPF as follows: Grade A—"transient pancreatic fistula", it has no clinical impact; Grade B—required a change in management or adjustment in the clinical pathway; Grade C—a major change in clinical management or deviation from the normal clinical pathway. Grade B and C were defined as "clinical pancreatic fistula".

RCT regarding the operative technique to prevent pancreatic fistula after pancreaticoduodenectomy (PD)

Several clinical trials regarding operative technique were performed to prevent pancreatic fistula after PD as follows: (I) pancreaticojejunostomy (PJ) versus pancreaticogastrostomy (PG); and (II) pancreatic stent.

PJ versus PG

Both PJ and PG are established reconstructive procedures in PD for pancreatic or periampullary tumors. The meta-analysis of RCTs published in 2015 revealed a higher rate of pancreatic fistula after PD in PJ, when compared to PG (14). In this meta-analysis seven RCTs were reviewed, including 562 patients who underwent PG and 559 who underwent PJ. The pancreatic fistula incidence was significantly lower in the PG group than in the PJ group (11.2% *vs.* 18.7%, OR: 0.53, 95% CI: 0.38–0.75, P=0.0003). The overall mortality rate was 3.7% in the PG group and 3.9% in the PJ group (P=0.68). No significant differences regarding overall morbidity and mortality were found between PJ and PG. PG has been thought to be safer than PJ for the following reasons: (I) the gastric acid environment inhibits the activation of pancreatic enzymes; (II) the proximity of the stomach to the pancreatic remnant decreases tension on the anastomosis; (III) the rich gastric vascular supply reduces the tendency for ischemia of the anastomosis (15-17). However, there are some limitations in this meta-analysis as follows; (I) the type of intervention and the indications for surgery which are different among seven RCTs may lead to different results; (II) the definition of pancreatic fistula varied among these RCTs may cause the different decision of pancreatic fistula among each institution. There were nine RCTs to examine that PG reduces the incidence of pancreatic fistula comparing PJ (*Table 1*) (17-25). Afterward, a multicenter prospective randomized controlled trial comparing PG with PJ from Germany was published in 2015 (25). The impact of study was the currently largest (n=440) multicenter prospective randomized controlled trial comparing PG with PJ regarding postoperative complications including pancreatic fistula and long-term pancreatic function. The incidence of grade B/C pancreatic fistula after PJ was similar to that after PG (PJ: 22% *vs.* PG: 20%, P=0.617). On the other hand, this study reported that PG was associated with a significantly increased rate of postpancreatectomy hemorrhage compared to PJ (PJ: 12% *vs.* PG: 20%, P=0.023), although there was no significant difference regarding overall morbidity and mortality between PJ and PG.

Regarding long-term pancreatic function between PJ and PG, two RCT have demonstrated that pancreatic exocrine insufficiency is more severe after PJ than PG (23,25). In contrast, one RCT has reported conflicting long-term outcomes regarding pancreatic function (24). However, pancreatic exocrine function in these RCTs was not measured directly. Alternatively, surrogate parameters including steatorrhea, body weight loss, and stool elastase level have represented pancreatic exocrine function indirectly. Moreover, surrogate parameters used for pancreatic exocrine function were different in each study. A furthermore large multicenter trial is required to evaluate long-term pancreatic function between PJ and PG.

Pancreatic duct stent in PJ

The impact of pancreatic duct stent to reduce pancreatic fistula after PD remains still controversial. There are three types for procedures of pancreatic duct stent as follows; lost stent, external stent and no stent. However, it remains unclear which is best procedure to reduce pancreatic fistula. There were five RCTs regarding pancreatic duct stent following PJ to prove the hypothesis that stent reduces the incidence of pancreatic fistula (*Table 2*) (10,26-29).

At first, three RCTs regarding external pancreatic duct stent versus no stent were reviewed. Poon *et al.* reported that pancreatic fistula occurred in 6.7% of patients with external drainage stent, and in 20% with no stent (P=0.032) in RCT which compared external drainage stent (n=60) with no stent (n=60) (10). However, this study included both soft and hard pancreatic parenchyma. Soft pancreas is well known to cause higher incidence of pancreatic fistula after PD than hard pancreas. Soft pancreas has been reported to be one of the risk factors for pancreatic fistula. In 2011, Pessaux *et al.* performed RCT to evaluate the impact of external duct stent among high-risk patients with soft pancreas or a non-

Table 1 Summary of nine randomized controlled trials regarding pancreaticogastrostomy versus pancreaticojejunostomy in PD

Authors	Settings	Years	Variable	Sample size	Definition of PF†	PF (%)	P value
Yeo *et al*. (17)	Single center	1995	PG	73	>50 mL of amylase-rich drainage fluid	12.3	NS
			PJ	72	after POD10 or pancreatic leakage	11.1	
					demonstrated radiographically		
Duffas *et al*. (18)	Multicenter	2005	PG	81	Chemically, 4 times normal serum amylase	16.0	NS
			PJ	68	level on POD3, clinically and radiologically	20.0	
					leak by fistulography		
Bassi *et al*. (19)	Single center	2005	PG	69	Any clinical significant output of fluid, rich	13.0	NS
			PJ	82	amylase confirmed by fistulography	16.0	
Fernández-Cruz	Single center	2008	PG	53	ISGPF‡	4.0§	<0.001
et al. (20)			PJ	55		18.0§	
Wellner *et al*. (21)	Single center	2012	PG	59	ISGPF‡	10.0§	0.775
			PJ	57		12.0§	
Topal *et al*. (22)	Multicenter	2013	PG	162	ISGPF‡	8.0§	0.002
			PJ	167		19.8§	
Figueras *et al*. (23)	Single center	2013	PG	65	ISGPF‡	15.0	0.014
			PJ	58		34.0	
El Nakeeb *et al*. (24)	Single center	2014	PG	45	ISGPF‡	22.2	0.796
			PJ	45		20.0	
Keck *et al*. (25)	Multicenter	2016	PG	171	ISGPF‡	20.0§	0.617
			PJ	149		22.0§	

†, pancreatic fistula; ‡, pancreatic fistula is defined according to the International Study Group of Pancreatic Surgeons (ISGPF) in its pancreatic fistula recommendation; §, the rate of ISGPF grade B/C. PD, pancreaticoduodenectomy; PG; pancreaticogastrostomy, PJ; pancreaticojejunostomy; NS, not significant.

Table 2 Summary of five randomized controlled trials regarding pancreatic duct stent in PD

Authors	Settings	Years	Variable	Sample size	Definition of PF†	PF (%)	P value
Winter *et al*. (26)	Single center	2006	Internal stent	115	>50 mL/day amylase-rich (3 times	11.3	NS
			No stent	119	serum level) on day 7 or more after	7.6	
					surgery		
Poon *et al*. (10)	Single center	2007	External stent	60	>10 mL/day (3 times serum level) more	6.7	0.036
			No stent	60	than 3 days after surgery	20.0	
Tani *et al*. (27)	Single center	2010	Internal stent	50	ISGPF‡	26.0	NS
			External stent	50		20.0	
Pessaux *et al*. (28)	Multicenter¶	2011	External stent	77	ISGPF‡	26.0	0.030
			No stent	81		46.0	
Motoi *et al*. (29)	Single center	2012	External stent	46	ISGPF‡	6.0§	0.040
			No stent	47		22.0§	

†; pancreatic fistula; ‡; pancreatic fistula is defined according to the International Study Group of Pancreatic Surgeons (ISGPF) in its pancreatic fistula recommendation; §, the rate of ISGPF grade B/C; ¶, only patients with soft pancreas and a diameter of P-duct less than 3 mm are enrolled. PD, pancreaticoduodenectomy; NS, not significant.

dilated duct less than 3 mm (28). The study has reported that external pancreatic duct stent significantly reduced pancreatic fistula compared to no stent: 20 of 77 (26%) in external pancreatic duct stent group versus 34 of 81 (42%) in no stent group (P=0.03). Moreover, the stent group significantly reduced morbidity compared to no stent group (41.5% *vs.* 61.7%, P=0.01). Similarly, Motoi *et al.* also reported that among patients with a non-dilated duct, external pancreatic duct stent significantly reduced clinically relevant pancreatic fistula compared to no stent: two of 21 (10%) versus eight of 20 (40%) (P=0.033) (29). Pancreatic duct stent may protect PJ by diverting pancreatic juice away from the anastomosis, to improve long-term pancreatic duct patency, and to facilitate precise suture placement.

On the other hands, the impact of internal pancreatic duct stent remains still unclear. Winter *et al.* has reported that internal pancreatic duct stent did not reduce the incidence of pancreatic fistula, compared to no stent (11.3% in internal pancreatic duct stenting; n=115 versus 7.6% in no stent; n=119) (26). However, in this study, the technique of PJ anastomosis was not standardized as the use of duct-to-mucosa or invagination technique. The invagination technique is chosen in PJ for a small pancreatic duct which is more difficult for duct-to-mucosa. A bias of surgeons in selecting the anastomotic technique may influence outcomes in this study. Moreover, external stent may decrease the incidence of stent migration or offer a better diversion of pancreatic juice away from anastomosis compared to internal stent. However, Tani *et al.* has reported that no difference was found between external and internal stents regarding short-outcomes including the incidence of pancreatic fistula (27). It remains still controversial which is better external stent or internal stent. Meta-analysis has reported that pancreatic duct stent did not reduce the incidence of pancreatic fistula and other complications in PD compared with no stent (30). A large multicenter randomized controlled trial for standardized anastomotic techniques for PD is required to conclusively evaluate the benefits of using pancreatic duct stents.

RCT regarding the operative technique to prevent pancreatic fistula after distal pancreatectomy (DP)

DP is a procedure for treatment both benign and malignant diseases of the body and tail of the pancreas. In an effort to reduce the incidence of PF after DP, surgeons have attempted various surgical techniques to transect pancreatic parenchyma including a hand-sewn closure, stapler closure, scalpel, electrocautery or ultrasonic devices. However, appropriate procedure to transect the pancreas during DP remains still controversial. *Table 3* summarizes RCTs regarding procedure to prevent pancreatic fistula after DP (31-36).

Stapler closure has recently become a standard technique for pancreatic stump closure. The meta-analyses on hand-sewn suture and stapler closure reported by Knaebel *et al.* showed that stapler closure (22.8%) had reduced pancreatic fistula more than hand-sewn suture (34.9%) (37) and those reported by Zhou *et al.* showed that stapler closure (22.1%) had reduced pancreatic fistula more than hand-sewn suture (31.2%) (38). These two reports of meta-analyses demonstrated that stapler closure in DP tended to reduce pancreatic fistula as compared to manual suturing, but could not prove that stapler closure was statistically useful. In 2011, the results of RCT of hand-sewn suture and stapler closure were published (31). However, the multicenter randomized DISPACT trial found that stapler closure did not significantly reduce the incidence of pancreatic fistula after DP in comparison to hand-sewn closure. In this study, 352 patients were randomized both treatment groups, 177 patients were stapler group, 175 patients were another group. The incidence of pancreatic fistula did not differ between both groups (stapler closure; 32% *vs.* hand-sewn; 28%, OR: 0.84, 95% CI: 0.53–1.33, P=0.56). Afterward, there are RCTs regarding absorbable material (32,34,35) or seromuscular patch (33) to reinforce the staple line. In 2012, it has been reported that the resection with a stapler having reinforcing absorbable materials significantly reduced clinically relevant pancreatic fistula (32). However, in two RCTs, an absorbable fibrin sealant patch (TachoSil) to stapling technique did not reduce the incidence of pancreatic fistula. Montorsi *et al.* have reported the incidence of pancreatic fistula was not significantly different between groups (with TachoSil group; 62% *vs.* without TachoSil group; 68%, P=0.267) in a multicenter, randomized, controlled trial (34). Park *et al.* also examined a similar prospective, multicenter, randomized controlled study (35). In this RCT, the incidence of clinically relevant postoperative complications (grade B and C, ISGPF) (with TachoSil group; 22.9% *vs.* without TachoSil group; 28.3%, P=0.536). These two studies demonstrated that the TachoSil patch did not reduce the incidence of pancreatic fistula after DP. TachoSil had no significant effect on the incidence of pancreatic fistula. On the other hand, a RCT has reported that covering the stapled pancreatic remnants with seromuscular patch significantly decreased the overall

Table 3 Summary of six randomized controlled trials regarding resection of pancreatic parenchyma in DP

Authors	Settings	Years	Variable	Sample size	Definition of PF†	PF (%)	P value
Diener *et al*. (31)	Multicenter	2011	Stapler	177	ISGPF‡	32.0	NS
			Hand-sewn	175		28.0	
Hamilton *et al*. (32)	Single center	2012	Stapler	46	ISGPF‡	20.0§	0.0007
			Stapler with mesh	54		1.9§	
Oláh *et al*. (33)	Single center	2009	Stapler	35	ISGPF‡	30.0	NS
			Stapler with a seromuscular patch	35		12.0	
Montorsi *et al*. (34)	Multicenter	2012	Standard closure¶	130	ISGPF‡	68.0	NS
			Standard closure with TachoSil	145		62.0	
Park *et al*. (35)	Multicenter	2015	Stapler	53	ISGPF‡	54.7	NS
			Stapler with TachoSil	48		70.8	
Kawai *et al*. (36)	Multicenter	2015	stapler	61	ISGPF‡	37.7	NS
			Pancreaticojejunostomy	62		38.7	

†, pancreatic fistula; ‡, pancreatic fistula is defined according to the International Study Group of Pancreatic Surgeons (ISGPF) in its pancreatic fistula recommendation; §, the rate of ISGPF grade B/C; ¶, standard closure: by stapler or by scalpel and hand-sewn suture. DP, distal pancreatectomy; NS, not significant.

rate of pancreatic-related complications, although the rates of clinically relevant postoperative complications (grade B and C, ISGPF) were comparable between two groups (33).

A multicenter randomized controlled trial has evaluated whether PJ of pancreatic stump decreases the incidence of pancreatic fistula after DP compared with stapler technique in a multicenter randomized controlled trial (36). This RCT demonstrated that PJ of the pancreatic stump during DP does not reduce pancreatic fistula compared with stapler closure. However, this study has reported that PJ of pancreatic stump in thickness of pancreas greater than 12 mm tended to reduce the incidence of clinically relevant pancreatic fistula compared to stapler closure (22.2% of the stapler closure group *vs.* 6.2% of the PJ group; P=0.080).

Efficacy the use of somatostatin or its analogues after pancreatic surgery

Somatostatin and somatostatin analogues, including octreotide and vapreotide, have well-recognized inhibitory effects on pancreatic exocrine secretion. Therefore, somatostatin or octreotide have been used as prophylactic agents to prevent pancreatic fistula after pancreas resection. *Table 4* summarizes RCTs regarding the administration of somatostatin and somatostatin analogues after pancreatic surgery. Two RCTs reported that prophylactic somatostatin or octreotide significantly reduced the incidence of pancreatic fistula after PPPD (39,40). On the other hand, four recent RCTs reported that the use of somatostatin analogues including octreotide and vapreotide, did not reduce pancreatic fistula after pancreas surgery (41-45). A meta-analysis regarding the benefit of somatostatin and its analogues reported that these agents reduced overall morbidity (P=0.003) and pancreas-specific complications (P=0.002), but did not reduce the incidence of clinically relevant pancreatic fistula after pancreatic surgery (47). In contrast, another meta-analysis report concluded that these agents didn't have advantages of utility for mortality, re-operation rate, and hospital stay, and the incidence of clinical pancreatic fistula after pancreatic surgery (48). Recently, one RCT reported that pasireotide which is another long-acting somatostatin analogue significantly reduced the incidence of pancreatic fistula after pancreatic surgery (46). As the reason to reduce pancreatic fistula, the report discussed that pasireotide has a long half-life and a strong affinity to some SSTR-subtypes compared to other somatostatin analogues. The impact of somatostatin and its analogues to reduce pancreatic fistula after pancreatic surgery remains controversial, as study design is heterogeneity by each study. Furthermore large multicenter RCTs are required to clarify the benefits of somatostatin and its analogues after pancreatic surgery.

Conclusions

Consensus on the best way to prevent pancreatic fistula after

Table 4 Summary of eight randomized controlled trials regarding administration of somatostatin and somatostatin analogues after pancreatic surgery

Authors	Years	Variable	Procedure	Sample size	Definition of PF†	PF (%)	P value
Shan *et al*. (39)	2003	Somatostatin	PD	27	>10 mL/day (3 times serum level) more	22.0	<0.050
		control		27	than 7 days after surgery	48.0	
Gouillat *et al*. (40)	2001	Somatostatin	PD	38	>100 mL/day (5 times serum level) more	5.0	0.047
		control		37	than 3 days after surgery	22.0	
Suc *et al*. (41)	2004	Octreotide	PD and DP	122	3 times serum level more than 3 days	11.0	NS
		control		108	after surgery	8.0	
Sarr (42)	2003	Vapreotide	PD and DP	135	>30 mL/day (5 times serum level) more	30.4	NS
		control		140	than 5 days after surgery	26.4	
Yeo *et al*. (43)	2000	Octreotide	PD	104	>50 mL/day amylase-rich (3 times serum	11.0	NS
		control		107	level) on day 10 or more after surgery	9.0	
Lowy *et al*. (44)	1997	Octreotide	PD	57	>200 mL/day (3 times serum level) more	12.0	NS
		control		153	than 3 days after surgery	6.0	
Fernández-Cruz *et al*. (45)	2013	Octreotide	PD	32	ISGPF‡	6.0§	NS
		control		30		10.0§	
Allen *et al*. (46)	2014	Pasireotide	PD and DP	152	ISGPF‡	11.0	0.002
		control		148		25.0	

†, pancreatic fistula; ‡, pancreatic fistula is defined according to the International Study Group of Pancreatic Surgeons (ISGPF) in its pancreatic fistula recommendation; §, the rate of ISGPF grade B/C. PD, pancreaticoduodenectomy; DP, distalpancreatectomy; NS, not significant.

pancreatic surgery remains still controversial. However, several RCTs steadily clarify a useful procedure to reduce the incidence of pancreatic fistula after pancreatic surgery. Therefore, further RCTs to study innovative approaches remain a high priority for pancreatic surgeons to prevent pancreatic fistula after pancreatic surgery.

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Footnote

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