Systematic Review and Meta-Analysis of Somatostatin Analogues in the Prevention of Postoperative Complication after Pancreaticoduodenectomy

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Key Words

Pancreaticoduodenectomy · Somatostatin · Octreotide ·
Pancreatic fistula · Systematic review

Abstract

Background: The use of somatostatin analogues (SAs) following pancreaticoduodenectomy (PD) is controversial.

Method: Literature databases were searched systematically for relevant articles. A meta-analysis of all randomized controlled trials (RCTs) evaluating prophylactic SAs in PD was performed. **Results:** Fifteen RCTs involving 1,352 patients were included. There was a trend towards reduced incidences of pancreatic fistulas ($p = 0.26$), clinically significant pancreatic fistulas ($p = 0.08$), and bleeding ($p = 0.05$) in prophylactic SAs group. In subgroup analyses, prophylactic somatostatin significantly reduced the incidence of pancreatic fistulas ($p = 0.02$), with a nonsignificant trend toward reduced incidence of clinically significant pancreatic fistulas ($p = 0.06$). Pasireotide significantly reduced the incidence of clinically significant pancreatic fistulas ($p = 0.03$). Octreotide had no influence on the incidence of pancreatic fistulas. **Conclusion:** The current best evidence suggests prophylactic treatment with somatostatin or pasireotide has a potential role in reducing the incidence of pancreatic fistulas, while octreo-

tide had no influence on the incidence of pancreatic fistulas. High-quality RCTs assessing the role of somatostatin and pasireotide are required for further verification.

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Introduction

Pancreaticoduodenectomy (PD) remains a high-risk operation to this day [1]. Pancreatic fistula (PF) is the leading cause of morbidity and mortality after PD [2, 3]. To reduce the incidence of PF, various methods have been proposed, including either technical or pharmacologic approaches [4]. Various technical improvements, such as external stent drainage of the pancreatic duct [5], pancreaticogastrostomy [6], have been successfully proven in reducing the incidence of PF after PD. However, the efficacy of somatostatin and its analogues (SAs), such as octreotide, vapreotide, and lanreotide, in prevention of PF after PD continues to be disputed.

Several randomized controlled trials (RCTs) have been conducted to address the controversy and concerns,

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yet the results were quite conflicting. Some studies confirmed the preventive effect; while the others did not support it. In recent years, there have been several meta-analyses that synthesized data obtained from the published RCTs to evaluate the efficacy of SAs. Nevertheless, most of the previous meta-analyses studied a mix of different pancreatic surgical procedures (PD, distal pancreatectomy, etc.) and did not evaluate the efficacy of SAs in PD specifically [7–10]. It should be noted the type of surgery could influence the rate of PF development. SAs may have different effects on different surgical procedures. Only one meta-analysis conducted 5 years ago attempted to evaluate the efficacy of SAs in preventing postoperative complication after PD [11]. However, this meta-analysis had used the inappropriate effect size (odds ratio), where the risk ratio would be more appropriate. In addition, this meta-analysis also included mixed pancreatic resection population. All of these meta-analyses were likely to introduce biases.

Although some surgical centers did not use SAs for prevention of complication after PD, SAs prophylaxis was still popular in many clinical settings [12–14]. As there is still some controversy with regard to the use of SAs in PD and several new RCTs are available, we conducted an up-to-date meta-analysis to provide the current best evidence on this topic.

Methods

Identification and Selection of Studies

Relevant studies were identified and selected by searching the databases, including: (1) Medline, Embase, Science Citation Index and Cochrane controlled trials register (updated to July 2013) under the search words ‘pancreaticoduodenectomy’ or ‘PD’ or ‘pylorus-preserving pancreaticoduodenectomy’ or ‘PPPD’, and ‘somatostatin’ or ‘octreotide’ or ‘vaptotide’ or ‘lanreotide’ or ‘pasireotide’, and ‘randomized controlled trial’ or ‘RCT’. (2) A review of reference bibliographies from original research articles and reviews. No language or date limitations were imposed.

The following inclusion criteria were applied: (1) Study design: randomized controlled trials (RCTs), including multicenter trials; (2) Study population: patients undergoing PD (including PPPD); (3) SAs should be administrated as prophylaxis; (4) Each study should contain information on incidences of postoperative PF. The following exclusion criteria were applied: (1) Studies compared two groups, both submitted to SAs with different dosage or route of the same SAs, or with different SAs; (2) Comparing SAs with other prophylactic intervention; (3) Studies including mixed pancreatic resection population (PD, distal pancreatectomy and pancreaticojejunostomy), without reporting specific PD outcomes. In the case of sequential or multiple publications of analyses of the same data or overlapping data sets, the publication that reported data from the largest or most recent study was included [15].

Data Extraction

Data were extracted from each study by two authors (Jin and Zhou) independently according to a predesigned protocol. Following data were recorded: (1) Basic characteristics: first author, year of publication, country, number of patients in each arm, sample size, mean age, administration methods of SAs, definition of pancreatic fistula; (2) Details in study design: method of randomization, blinding (single, double or none), withdrawal and dropouts; (3) Primary outcomes: incidences of PF, incidences of clinically significant PF (defined as PF require alteration in the management of the patient), and mortality rates; (4) Secondary outcomes: incidences of abdominal infection, delayed gastric emptying, bleeding, pulmonary complication, overall complication, reoperation and length of hospital stay.

Quality Assessment

We applied the Jadad composite scale to assess the methodological quality of studies included in the meta-analysis [16]. This is a 5-point quality scale, which evaluates the studies based on perfect randomization, proper blinding, and adequate descriptions of withdrawals and dropouts. If the Jadad score of a study is more than or equal to 3, we considered it a high-quality study. Quality assessment was independently performed by two authors (Jin and Zhou). Each included study was given an overall quality score based on the Jadad composite scale. Any disagreement was resolved by discussion and consensus.

Statistical Methods

The risk ratio (RR) was used as the effect size for dichotomous data, while weighted mean difference (WMD) was used for continuous data. Summary RR (or WMD) and their corresponding 95% confidence intervals (CI) were estimated by fixed effect (Mantel-Haenszel) or random effect (DerSimonian and Laird) models [17, 18]. Tests for heterogeneity were performed with each meta-analysis using the Cochran Q statistic and the I^2 test, with $p < 0.05$ indicating significant heterogeneity. Random effect model was performed when heterogeneity was present. To check for publication bias, a funnel plot was constructed using Egger’s linear regression method [19]. Statistical analyses were performed using Revman 5.0 and STATA 9.0 software packages. A p value < 0.05 was considered statistically significant.

Results

Characteristics of Included Studies

1,184 records were identified by the search strategy; 1,159 records were excluded because of the reasons shown in figure 1. Of the 25 potentially appropriate studies [20–44] seven were excluded for reporting no explicit outcome of PD [20–25, 27] one for duplicate publication [26] one for comparing somatostatin with octreotide [29] one for using octreotide in the control group [28]. Finally, 15 RCTs were included in the meta-analysis (table 1) [30–44].

The meta-analysis involved 1,352 patients: 693 were randomized to SAs group and 659 to control group. Elev-

Fig. 1. Flowchart of study screening according to PRISMA guidelines.

en studies were single-center trials, while the other four studies were multicenter trials. The mean age ranged from 52.5 to 69.0 years. Five studies used somatostatin, while nine studies used octreotide and one study used pasireotide. In terms of surgical approach, eight studies used classic PD, one study used PPPD in all participants, and the other studies used both PD and PPPD. Definition of PF varies among different studies (table 1). The methodological quality scores of included trials ranged from 1 to 5 (table 2).

Results of Meta-Analyses

Primary Outcomes. After pooling all the trials, 198 PFs occurred (198/1,133, 17.5%), 96 in the SAs group (96/583, 16.5%) and 102 in the control group (102/550, 18.5%). The pooled RR was 0.87 (95% CI 0.69–1.11). Eighty five clinically significant PFs occurred (85/658, 13.0%), 36 in the SAs group (36/337, 10.7%) and 49 in the control group (49/321, 15.3%). The pooled RR was 0.70 (95% CI 0.47–1.05). Thirty four deaths occurred (34/865, 3.9%), 21 in the SAs group (21/442, 4.8%) and 13 in the control group (13/423, 3.1%). The pooled RR was 1.42 (95% CI 0.76–2.65) (fig. 2).

Secondary Outcomes. There were no significant differences between the two groups in incidences of abdominal

infection (RR 0.78, 95% CI 0.44–1.37), delayed gastric emptying (RR 0.84, 95% CI 0.55–1.29), bleeding (RR 0.45, 95% CI 0.20–1.01), pulmonary complication (RR 0.90, 95% CI 0.31–2.57), overall complication (RR 0.89, 95% CI 0.71–1.11) and re-operation rate (RR 1.22, 95% CI 0.61–2.45). In addition, there was no difference in the length of hospital stay (WMD –1.32, 95% CI –4.22 to 1.58) between the two groups (fig. 3).

Subgroup Analyses

In subgroup analyses, prophylactic somatostatin significantly reduced the incidence of pancreatic fistulas ($p = 0.02$), with a nonsignificant trend toward the reduced incidence of clinically significant pancreatic fistulas ($p = 0.06$). Pasireotide significantly reduced the incidences of clinically significant pancreatic fistulas ($p = 0.03$). Octreotide had no influence on the incidence of pancreatic fistulas (table 3).

Publication Bias

We assessed the publication bias based on the results of PF and perioperative mortality. No evidence of publication bias existed in the studies included in the meta-analysis, based on the egger's publication bias plots (fig. 4).

Table 1. Characteristics of included studies

Author, year	No. of patients	Mean age	Intervention	Administration methods	Surgical approach	Pancreatic fistula definition	Medical center or clinic	Final pathology	PF	
									SAs group	control group
Allen et al. [44], 2014	111/109	NS	Pasireotide	900 µg s.c. per 12 h for 7 days	PD	Clinical signs and symptoms of pancreatic fistula, with ARF >50 ml per day after postoperative day 10, radiologic, endoscopic, or operative intervention required	Single-center	NS	10.0% (11/110)	21% (23/109) (34/220)
Beguiristain et al. [30], 1995	21/14	59.4	Somatostatin	4.5 mg i.v. per 24 h for 7 days	PD	≥10 ml fluid with amylase concentration of >5 NSA	Single-center	Malignancy (85.7%); Chronic pancreatitis (8.6%); Other tumor	20.0% (2/21)	20.0% (5/14) (7/35)
Briceno et al. [31], 1998	16/18	52.5	Octreotide	100 µg s.c. per 8 h for 7 days	PD	≥50 ml/day, ARF for >2 weeks	Single-center	Malignancy (82.4%); Chronic pancreatitis (0/16)	0.0% (0/16)	27.8% (5/18) (14.7% (5/34)
Buccoliero et al. [32], 1992	8/8	58.2	Somatostatin	6 mg i.v. per 24 h for 7 days	PD	NS	Single-center	Neoplasm (100%)	0.0% (0/8)	12.5% (1/8) (6.3% (1/16)
Fernández et al. [33], 2013	32/30	69	Octreotide	100 µg s.c. per 8 h for 10 days	PPPD	Any volume after day 3 with amylase content >3 times NSA	Single-center	Malignancy (91.9%); Other tumor	6.25% (2/32)	10.0% (3/30) (8.1% (5/62)
Gouillat et al. [34], 2001	38/37	60.2	Somatostatin	6 mg i.v. per 24 h for 6 days; 3 mg i.v. per 24 h in day 7	PD and PPPD	>100 ml/day ARF (>5 times NSA), after day 3, persisting after day 12, or in association with temperature >38°C or symptoms requiring surgery, drainage or intensive care	Multi-center	Malignancy (81.3%); Chronic pancreatitis (5.3%); Other tumor	10.5% (4/38)	27.0% (10/37) (18.7% (14/75)
Hesse et al. [35], 2005	41/39	NS	Octreotide	100 µg s.c. per 8 h for 7 days	PD and PPPD	>100 ml/day of ARF (>5 times NSA), after day 3, persisting after day 7, with temperature >38°C and pre-septic conditions	Single-center	Malignancy (85%); Chronic pancreatitis (3.8%); Other tumor	12.2% (5/41)	7.70% (3/39) (10.0% (8/80)
Klempa et al. [36], 1991	12/12	56.5	Somatostatin	6 mg i.v. per 24 h for 6 days	PD	NS	Single-center	Malignancy (100%)	8.33% (1/12)	16.7% (2/12) (12.5% (3/24)
Kollmar et al. [37], 2008	35/32	62.3	Octreotide	100 µg s.c. per 8 h for 7 days	PD and PPPD	Any volume after day 3 with amylase content >3 times NSA	Single-center	Malignancy (49.3%); Chronic pancreatitis (23.9%); Other tumor	25.7% (9/35)	18.8% (6/32) (22.4% (15/67)
Kurumboor et al. [38], 2012	24/21	NS	Octreotide	100 µg s.c. per 8 h for 5 days	PD	NS	Single-center	NS	75.0% (18/24)	76.2% (16/21) (75.6% (34/45)
Lowy et al. [39], 1997	57/53	63.0	Octreotide	150 µg s.c. per 8 h for 5 days	PD	ARF >2.5 times NSA, ≥day 3 with fever or leukocytosis or sepsis	Single-center	Malignancy (95.5%); Benign tumor	28.1% (16/57)	20.8% (11/53) (24.5% (27/110)

Table 1. (continued)

Author, year	No. of patients	Mean age	Intervention	Administration methods	Surgical approach	Pancreatic fistula definition	Medical center or clinic	Final pathology	PF		
									SAs group	control group	total
Montorsi et al. [40], 1995	76/67	NS	Octreotide	100 µg s.c. per 8 h for 7 days	PD	>10 ml/day ARF (>3 times NSA) after day 3	Multi-center	NS	10.5% (8/76)	14.9% (10/67)	12.6% (18/143)
Shan et al. [41], 2003	27/27	67.0	Somatostatin	6 mg i.v. per 24 h for 7 days	PD and PPPD	>10 ml/day ARF (>3 times NSA), for >7 days	Single-center	Malignancy (81.5%); Other tumor	7.4% (2/27)	7.4% (2/27)	7.4% (4/54)
Suc et al. [42], 2004	92/85	NS	Octreotide	100 µg s.c. per 8 h for 10 days	PD and PPPD	Any volume with ARF >4 times NSA for 3 days or clinical/radiological anastomotic leak	Multi-center	NS	19.6% (18/92)	21.2% (18/85)	20.3% (36/177)
Yeo et al. [43], 2000	104/107	64.7	Octreotide	250 µg s.c. per 8 h for 7 days	PD and PPPD	>50 ml/day ARF (>3 times NSA) on or after day 10 or radiological pancreatic anastomosis disruption	Multi-center	Malignancy (72.0%); Chronic pancreatitis (10.4%); Other tumor	10.6% (11/104)	9.34% (10/107)	10.0% (21/211)

PD = Pancreaticoduodenectomy; PPPD = pylorus-preserving pancreaticoduodenectomy; NSA = normal serum amylase; ARF = amylase rich fluid; PF = pancreatic fistula; NA = not report; SAs = somatostatin analogues.

Table 2. Jadad quality score of trials included in meta-analysis

Study	Randomized method	Double blinding	With withdrawals dropouts	Total
Allen et al. [44], 2014	2	2	1	5
Beguiristain et al. [30], 1995	1	0	0	1
Briceño et al. [31], 1998	1	1	0	2
Buccoliero et al. [32], 1992	2	0	0	2
Fernández et al. [33], 2013	2	2	1	5
Gouillat et al. [34], 2001	2	2	1	5
Hesse et al. [35], 2005	2	0	0	2
Klempa et al. [36], 1991	0	1	0	1
Kollmar et al. [37], 2008	2	2	1	5
Kurumboor et al. [38], 2012	1	1	0	2
Lowy et al. [39], 1997	1	0	0	1
Montorsi et al. [40], 1995	0	2	0	2
Shan et al. [41], 2003	2	1	0	3
Suc et al. [42], 2004	2	1	0	3
Yeo et al. [43], 2000	1	2	1	4

Discussion

PF formation remains the ‘Achilles heel’ of PD and continues to challenge surgeons since it is the main cause of postoperative morbidity and mortality [45]. Active exocrine secretion of pancreas is considered a major factor responsible for PF development, and its inhibition holds the promise of reducing the incidence of PF and its associated complications after PD. SAs are known to have inhibitory effects on exocrine secretion of pancreas [46]. These drugs had been presumed to reduce the rate of PF. The concept of using SAs to prevent complication after PD was introduced by Klempa et al. [47] in 1979. Since then, several groups of investigators had evaluated the administration of SAs for the prevention of complications after PD. Yet the results were quite conflicting. As there is still no definitive conclusion on this issue, it may be particularly germane to do such a systematic review to resolve this problem that is frequently encountered in the surgical community.

The main finding of our meta-analysis was that prophylactic treatment with somatostatin or pasireotide have a potential role in reducing the incidence of pancreatic fistulas, while octreotide had no influence on the incidence of pancreatic fistulas. It is worth noting that pasireotide has a longer half-life and a broader binding profile, decreases pancreatic exocrine secretions, and can be used for the prevention of postoperative pancreatic fistulas [48].

Fig. 2. Forest plot – somatostatin and its analogues vs. no intervention. Primary outcome: pancreatic fistula (**a**), clinically significant pancreatic fistula (**b**), perioperative mortality (**c**). (For figure 2c see next page.)

However, before drawing a conclusion, there are still lots of things we need to reconsider. First of all, although there was no statistical heterogeneity among included studies (except for length of hospital stay), we could not exclude the potential clinical heterogeneity. In fact, there was a wide variability in reported rates of PF after PD among included studies, with the rates of PF ranging

from 6.2 to 75.6% and the rates of clinically significant PF ranging from 8.1 to 20.0%. An important source of clinical heterogeneity may come from the variability in definition of PF. A more strict definition may result in a higher rate of PF, while a more compromised definition may lead to a lower rate of PF [49]. The same is true for clinically significant PF. The definition of clinically

c Perioperative mortality

a Abdominal infection

b Delayed gastric emptying

Fig. 3. Forest plot – somatostatin and its analogues vs. no intervention. Secondary outcome: abdominal infection (a), delayed gastric emptying (b).

c Bleeding

d Pulmonary complication

e Overall complication

Fig. 3. Forest plot – somatostatin and its analogues vs. no intervention. Secondary outcome: bleeding (**c**), pulmonary complication (**d**), overall complication (**e**).

f Re-operation

g Length of hospital stay

Fig. 3. Forest plot – somatostatin and its analogues vs. no intervention. Secondary outcome: re-operation (**f**), length of hospital stay (**g**).

Table 3. Subgroup analyses: comparison of somatostatin analogues vs. no intervention in outcomes

Somatostatin analogue	Outcome	No. of study	Experimental		Control		Analysis mode	Pooled effects (95% CI)	Test for heterogeneity, Chi-square test (p)	Z test for pooled effect size (p)
			events	total	events	total				
Somatostatin	PF	5	9	106	20	98	Fixed	0.42 (0.21–0.85)	1.23 (0.08)	2.41 (0.02)
	Clinically significant PF	1	2	38	8	37	Fixed	0.24 (0.06–1.07)		1.87 (0.06)
Octreotide	PF	9	87	477	82	452	Fixed	0.99 (0.76–1.27)	5.31 (0.72)	0.11 (0.91)
	Clinically significant PF	5	23	189	18	175	Fixed	1.17 (0.66–2.09)	2.30 (0.68)	0.54 (0.59)
Pasireotide	Clinically significant PF	1	11	110	23	109	Fixed	0.47 (0.24–0.92)	–	2.19 (0.03)

CI = Confidence interval; PF = pancreatic fistula.

Fig. 4. Egger's publication bias plots – pancreatic fistula rates (a), perioperative mortality rates (b).

significant PF lacks uniform definition before the ISGPF definition in 2005 [50]. Another source of clinical heterogeneity may be attributed to the differences in inclusion criteria. Some included studies did not recruit chronic pancreatitis patients, while the others recruited a large number of chronic pancreatitis patients. It is well known that patients who underwent PD for chronic pancreatitis have lower rates of PF, compared with patients who underwent PD for malignancy. Furthermore, PD for different malignancies may also result in different outcomes. However, given the limitation of the trials included, it is impossible to analyze these factors independently.

Last but not the least, the different rates of PF among included studies may be attributed to the surgical technique and experience of different surgeons, which were often ignored. Notably, delicate surgical technique and

other non-pharmacologic prophylactic procedures were more important because major complications, such as PF, were usually related to technical pitfalls. The outcome of PD is dependent on surgical experience and hospital volume [51]. To reduce the morbidity and mortality after PD, a policy of centralization may therefore be appropriate [52].

Patient-derived risk factors of PF after PD included soft pancreatic texture, small pancreatic duct and poor blood supply [53, 54]. These patients were clarified as high-risk. Some surgeons believed that the high-risk patients who underwent PD would benefit from prophylactic SA [12–14]. Unfortunately, a subgroup meta-analysis of high-risk patients cannot be performed because of limited data. However, the studies of Lowy et al. [39], Yeo et al. [43], and Shan et al. [41] showed that SAs could not reduce the rate of PF and other complications in patients at high-risk after PD. In addition, Fernández-Cruz et al. [33] further demonstrated no significant differences in median pancreatic juice output were found between SAs and placebo groups in high-risk patients (with a pancreatic duct diameter <5 mm). Thus, there is no solid evidence that SAs would reduce PF after PD in high-risk patients.

SAs seemed to be well-tolerated, and the adverse effects associated with the intervention were mainly minor adverse effects, such as pain at the injection site. However, downregulation of digestive enzyme secretion by SAs could contribute to the prolonged time to resume intestinal transit and increase delayed gastric emptying [26]. Furthermore, prophylactic SAs were usually used for 6 or 7 days in the included trials, and the high cost was a big concern.

It is possible that unpublished articles, such as scientific dissertations, may be missed because only published studies can be involved in the meta-analysis. However, by constructing funnel plots by Egger's linear regression methods, we found no publication bias.

In conclusion, the current best available evidence suggests prophylactic treatment with somatostatin or pasireotide have a potential role in reducing incidence of pancreatic fistulas, while octreotide had no influence on the incidence of pancreatic fistulas. High-quality RCTs assessing the role of somatostatin and pasireotide are required for further verification.

Acknowledgment

Declaration of Personal Interests: None.

Funding

This work was supported by the National Natural Science Foundation of China (No. 31100681), Shanghai nanotechnology program (11nm0504800) and Shanghai Rising Star Program (No. 11CG42).

Disclosure Statement

None declared.

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Author Contribution

Kaizhou Jin, Haiyang Zhou and Zhiqian Hu designed study. Kaizhou Jin and Haiyang Zhou collected and analyzed data. Kaizhou Jin and Haiyang Zhou wrote the draft. Jian Zhang, Weijun Wang, Yanping Sun, Canping Ruan, Yi Wang and Zhiqian Hu revised it critically. All the authors approved the version to be published.

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