Systematic Review and Meta-Analysis

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Efficacy of the prophylactic use of octreotide for the prevention of complications after pancreatic resection

An updated systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: The use of octreotide prophylaxis in the prevention of complications after pancreatic resection remains controversial. The aim of this systematic review and meta-analysis was to evaluate the efficacy of octreotide prophylactic treatment to prevent complications after pancreatic resection.

Methods: Five databases (PubMed, Medline, SinoMed, Embase, and Cochrane Library) were searched for eligible studies from 1980 to November 2016 with the limitation of human subjects and randomized controlled trials (RCTs). Data were extracted independently and were analyzed using RevMan statistical software version 5.3 (Cochrane Collaboration, http://tech.cochrane.org/revman/download). Weighted mean differences (WMDs), risk ratios (RRs), and 95% confidence intervals (CIs) were calculated. Cochrane Collaboration risk of bias tool was used to assess the risk of bias.

Results: Twelve RCTs comprising 1902 patients were identified as eligible. The methodological quality of the trials ranged from low to moderate. A pooled analysis of effectiveness based on the data from each study revealed that octreotide could significantly reduce the rate of pancreatic fistula (PF) after pancreatic resection (RR = 0.75, 95% CI = 0.57–0.98, $P = .04$). The same findings were discovered in multicenter and European subgroups with a subgroup analysis; no obvious differences were noted in American, Asian, and single-center subgroup analyses. An equal effect was observed between the use or non-use of octreotide groups regarding mortality (RR = 1.24, 95% CI = 0.77–2.02, $P = .38$). Octreotide had no advantages in regards to mortality improvement. The total numbers of complications associated with the use or non-use of octreotide were similar (RR = 0.77, 95% CI = 0.58–1.03, $P = .08$). Among the high-risk group, octreotide was more effective in reducing complications (RR = 0.61, 95% CI = 0.46–0.82, $P = .0009$). Compared with the patients who did not receive prophylactic treatment, the patients who underwent pancreatic resection benefited from octreotide because it had better efficacy in preventing fluid collection and postoperative pancreatitis.

Conclusion: The prophylactic use of octreotide is suitable for preventing postoperative complications, especially PF and fluid collection as well as postoperative pancreatitis. However, no obvious differences were noted regarding mortality. In view of the clinical heterogeneity and varying definitions of PF, whether these conclusions are broadly applicable should be further determined in future studies.

Abbreviations: CIs = confidence intervals, DGE = delayed gastric emptying, DPPHR = duodenum-preserving pancreatic head resection, IQR = interquartile range, ISGPF = International Study Group of Pancreatic Fistula, ISGPS = International Study group on Pancreatic Surgery, Mesh = medical subject headings, PD = pancreaticoduodenectomy, PF = pancreatic fistula, PPPD = pylorus-preserving pancreaticoduodenectomy, RCTs = randomized controlled trials, RRs = risk ratios, SD = standard deviations, WMDs = weighted mean differences.

Keywords: complications, meta-analysis, pancreatic resection, prophylactic octreotide

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1. Introduction

In the pancreas, diseases that require surgical treatment primarily include pancreatic adenocarcinoma, benign tumor, and chronic pancreatitis. Early surgical treatment in chronic pancreatitis can not only improve the quality of life of patients to relieve pain and retain the internal and external secretion of pancreatic function but also effectively remove cancer risk factors.[1] As surgical approaches to the treatment of pancreatic disease have undergone a transformation over the past few decades, they have become a relatively safe method for various benign and malignant pancreatic diseases, with mortality rates below 5%.[2] However, patients undergoing surgical treatment also have a high incidence of complications; in particular, pancreatic fistula (PF) after pancreatic resection remains as high as 30% to 50%.[3–5] PFs are the most serious and common complications after pancreatic surgery.[6–8] Because these complications are mainly associated with exocrine pancreatic secretion, inhibiting the exocrine secretion of the pancreas is considered a suitable method to avoid PF development. Moreover, as early as 1979, Klempa et al[9] noted that inhibition of pancreatic exocrine secretion could reduce the incidence of PF.

Octreotide (SMS 201–995), a long-acting octapeptide analog of somatostatin, was synthesized to have more specific, more potent, and longer-acting inhibitory effects than native somatostatin.[10,11] In 1986, octreotide was considered useful in the prevention of postoperative complications after pancreatic resection.[12] It can powerfully inhibit basal and stimulated exocrine pancreatic secretion, making it more advantageous for clinical applications.[13] Octreotide has been recognized as one of the somatostatin analogs used in the prevention of PF after resection.[14] However, some different results have also been obtained.[15,16] Despite 30 years of octreotide clinical use in preventing postoperative complications, especially PF, evidence of the benefit of its use is still lacking, and there is currently no consensus regarding recommendations or guidelines. The efficacy of prophylactic octreotide in preventing postoperative complications remains speculative.

To further assess the existing evidence, we assessed the efficacy of prophylactic octreotide in the prevention of postoperative complications, particularly the formation of PF and mortality. We conducted an updated meta-analysis with a thorough search of the current literature to evaluate the efficacy of prophylactic octreotide for the prevention of postoperative complications after pancreatic resection.

2. Methods

Ethical approval or patient consent was not required since the present study was a review of previous published literature.

2.1. Search strategy and study selection criteria

A computerized search was conducted from 1980 to November 2016 with the PubMed, Medline, SinoMed, Embase, and Cochrane Library databases. The databases were queried for eligible literature using combinations of the following medical subject headings (MeSH): "pancreaticoduodenectomy or PD or pylorus-preserving pancreaticoduodenectomy or PPPD or pancreatic resection or pancreatectomy" and "octreotide or octreotide acetate or somatostatin analog" and "randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial." The detailed search strategy for each database was provided (see supplemental content, http://links.lww.com/MD/B795). The search was limited to human subjects. There was no language limitation. The titles and abstracts of potentially relevant studies identified by the computerized search were reviewed. Additionally, we reviewed abstracts from a conference of the Ihpba World Congress. Full-text articles were obtained for detailed evaluation, and eligible studies were included in the systematic review.

The inclusion criteria were the following: the study included outpatients who were of either sex, had a clinical and histological diagnosis of chronic pancreatitis, pancreatic adenocarcinoma, or other pancreatic-related benign tumor, and were undergoing elective pancreatic resections; octreotide should be administered as prophylaxis, with the aim of the trial being a comparison of the effectiveness of octreotide in preventing complications after pancreatic resection in the octreotide group and a placebo or no intervention in the control group; the method of administration should be subcutaneous, and outcomes included at least the incidence of postoperative PF, mortality, and other postoperative complications; and study designs should be randomized controlled trials (RCTs), including multicenter and single-center trials.

The exclusion criteria were the following: patient information data that were insufficiently clear; application of other drugs, such as different somatostatin analogs or therapies during the treatment.

2.2. Data collection and extraction

Two coauthors independently reviewed all titles and abstracts of the searched papers. Extracted data included the characteristics of the eligible studies, such as author, country, details of the study design, sample size, sex, mean age, interventions, incidences of postoperative PF, mortality, numbers of complications, and disease pathology. Discrepancies were resolved through discussion or with a third party to resolve conflicting evaluations. In 2 of the included studies, patients were stratified into high-risk (those with tumors in the pancreas or periampullary region) and low-risk (those with chronic pancreatitis) groups. Both the high-risk and low-risk groups had available data on PFs that were extracted and assessed in the study.

2.3. Outcome measures

The primary outcome was the incidence of PF after pancreatic surgery and mortality during the treatment. The analyses of overall occurrence of all grades PF (grades A, B, and C) and only to those having a clinical impact PF (only grades B and C) were conducted. Secondary outcomes were other postoperative complications, such as anastomosis leakage, abscess, fluid collection, shock, sepsis, pulmonary insufficiency, renal insufficiency, bleeding, and postoperative pancreatitis. Moreover, the adverse effects of the study drugs, had also been described.

2.4. Quality assessment and risk of bias

Two reviewers independently screened, extracted, and checked the research data to ensure consistency. The quality of trials that were designed with control and treatment groups was assessed using Review Manager (Version 5.3; The Cochrane Collaboration, Oxford, UK). The risk of bias for RCT studies was evaluated with Cochrane Collaboration Risk of Bias Tool. Seven parameters were used to evaluate the quality of each included study: random sequence generation, allocation concealment,

blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other risks. Items were judged as "low risk," "unclear risk," or "high risk." Any disagreement was resolved by a discussion, and a consensus was reached.

2.5. Statistical methods

In the systematic review, meta-analysis was conducted using Review Manager 5.3 software (Cochrane Collaboration, http://tech.cochrane.org/revman/download). For dichotomous outcomes in the extracted data, risk ratios (RRs) and 95% confidence intervals (CIs) were calculated, and weighted mean differences (WMDs) and 95% CIs were used for continuous outcomes. Heterogeneity was assessed using the Q test and I^2 test. Statistical significance was set at $P < .05$. If there was significant heterogeneity, $P < .05$ and $I^2 > 50\%$, if there was no significant heterogeneity, $P \geq .05$ and $I^2 \leq 50\%$. In view of the clinical and methodological heterogeneity across the studies, if the same results were obtained under these 2 models, a random-effects model was a more appropriate choice. When the interquartile range (IQR) and median were given instead of the standard deviation (SD), we converted the data using Hozo algorithm to estimate the SD.[17]

2.6. Subgroup and sensitivity analyses

Subgroup analyses based on the different study designs (multicenter or single-center), the geographical location (Europe, America, or Asia), and the pathology of the disease (low-risk stratum or high-risk stratum) were performed with available data to access the efficacy of the octreotide prophylactic treatment to prevent complications after pancreatic resection. The high-risk stratum included patients suffering from tumors such as pancreatic cancer, periampullary cancer, and endocrine tumor, while the low-risk stratum included patients who had chronic pancreatitis. We also performed sensitivity analysis to assess the stability of the results and investigate the influence of each study by omitting a single study sequentially. Publication bias was showed by funnel plot.

3. Results

3.1. Data extraction

Of the 1976 citations identified based on a study of the subject and a summary of the literature, 1922 articles were excluded because of duplication. After reviewing the title and abstract of the remaining 54 studies, only 30 full-text studies were evaluated for further assessment, and 18 obviously irrelevant records were excluded. Finally, 12 clinical studies satisfied the inclusion requirements.[18–29] A detailed study flow diagram is shown in Fig. 1.

3.2. Description of studies

All 12 of the assessed studies were in English. The meta-analysis involved a total of 1902 patients: 964 were randomized to the octreotide group, and 938 were randomized to the control group. Eight of the 12 studies were randomized placebo-controlled trials, and the remaining studies were RCTs of octreotide versus no treatment. Among the 12 identified studies, 6 were single-center trials conducted in the United States (1),[18] Belgium (1),[19] Switzerland (1),[20] Spain (1),[21] and India (2).[22,23] The other 6 studies were multicenter trials conducted in Germany (3),[24–26] Italy (1),[27] the United States (1),[28] and France (1).[29] The mean age ranged from 47.0 to 69.0 years. The majority of patients enrolled in the 10 studies had standard clinical diagnoses of pancreatic adenocarcinoma, endocrine tumor, periampullary tumor, chronic pancreatitis, and other pancreatic diseases

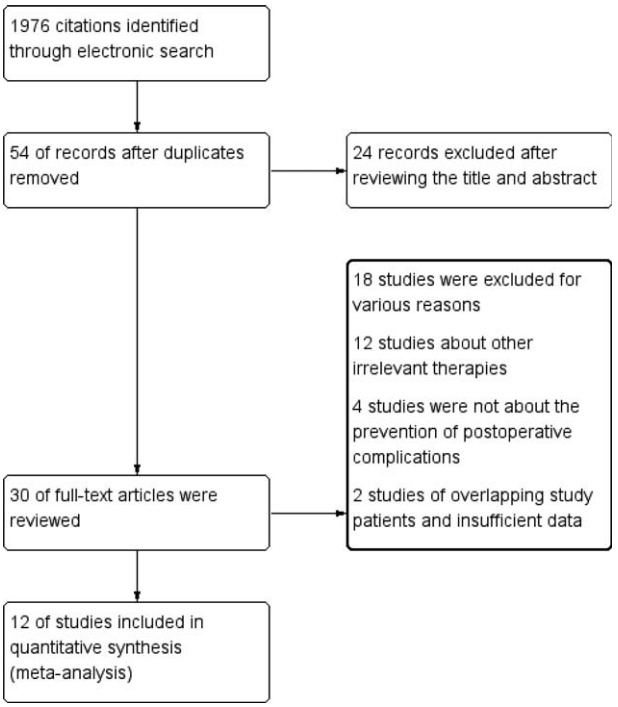

Figure 1. Flow diagram for the selection of randomized controlled trials included in the meta-analysis.

requiring surgical treatment.[18–22,24,25,27–29] Only 2 studies enrolled patients who suffered only from chronic pancreatitis.[23,26] The daily dose of octreotide ranged from 100 to 250 μg administered subcutaneously every 8 hours, and the duration of intervention ranged from 5 to 10 days. In addition, 2 included studies stratified patients into 2 groups, high-risk and low-risk patients, according to the characteristics of pancreatic pathology. Patients with tumors of the pancreas or periampullary region were in the high-risk group, and patients with chronic pancreatitis were in the low-risk group.[24,25] All the included studies evaluated the incidence of PF, mortality, and other related complications, and we extracted relevant useful data to conduct our analyses. The characteristics of the included studies are presented in Table 1.

3.3. Methodological assessment of study quality

The Cochrane Collaboration tool was used to assess the risk of bias of the included studies. The methodological quality assessment of the 12 included studies is presented in Fig. 2. The quality of these studies was low to moderate. All identified studies were RCTs, and randomization was performed according to a computer-generated random list or by means of a randomly generated number pattern in a majority of the trials. Six of the included studies were double-blind placebo-controlled trials,[20,24–28] 1 was a single-blind study,[29] and 1 was an open-label trial[19]; the remaining 4 studies did not mention whether they used a method of blinding that may introduce measurement bias.[18,21–23] The method of allocation concealment was not described in detail, giving rise to a high risk for selection and measurement bias. Thus, 6 out of 12 trials were single-center trials,[18–23] and the other 6 studies were multicenter trials,[24–29] which may also have been a source of bias. See Fig. 3.

3.4. Primary outcome: incidence of PF and mortality

From the aforementioned studies, a total of 341 patients suffered from PF (341/1902, 17.93%) after pancreatic resection: 143 PFs occurred in the octreotide group (143/964, 14.83%), and 198 occurred in the placebo group. Moderate heterogeneity among the studies was revealed ($I^2=49\%$), and the random-effects model was adopted in the analysis. The pooled RR was 0.75 (95% CI 0.57–0.98, $P=.04$). Grade B and C fistulas were identified as clinically significant PFs. Fifty-eight clinically significant PFs occurred (58/498, 11.65%): 29 in the octreotide group (29/258, 11.24%) and 29 in the placebo group (29/240, 12.08%). A pooled analysis revealed that there was no statistically significant difference between the 2 groups in the induction of clinically significant PF (RR = 0.91, 95% CI = 0.55–1.49, $P=.71$). See Figs. 4 and 5.

All identified studies reported on mortality, except 1.[22] Sixty-five deaths occurred (65/1857, 3.5%): 37 in the octreotide group (37/940, 3.9%), and 28 in the control group (28/917, 3.1%). A pooled analysis revealed that RR was 1.24 (95% CI 0.77–2.02, $P=.38$). No significant differences between the 2 groups were observed. See Fig. 6.

3.5. Secondary outcome: postoperative complications

After pooling all the trials, 8 studies were found to contain relevant data on patients with complications, comprising a total of 1456 patients. Specifically, 182 out of 731 patients who were administered octreotide before the operation reported complications, and 246 out of 725 patients in the control group showed side effects. A heterogeneity test revealed significant heterogeneity among the studies ($I^2=64\%$); thus, the random-effects model was used. The pooled analysis under the random-effects model indicated that there was no significant difference in the incidence of complications between the octreotide and control groups (RR = 0.77, 95% CI = 0.58–1.03, $P=.08$). The finding that the upper confidence limit for the RR barely exceeded 1.0 and that the horizontal block lay to the left of the vertical line indicated that the administration of octreotide preoperatively may reduce the rate of complications. See Fig. 7.

A pooled analysis of the complications showed that there was no significant difference between the 2 groups in anastomosis leakage, abscess, shock, sepsis, pulmonary insufficiency, renal insufficiency, bleeding, wound infection, and delayed gastric emptying. However, the administration of octreotide preoperatively significantly reduced the rates of fluid collection. In the result of inducing postoperative pancreatitis, given that the upper confidence limit for the RR barely exceeds 1.0, and that the horizontal block lies to the left of the vertical line, it indicates that prophylactic treatment of octreotide could reduced the incidence of postoperative pancreatitis. The detailed complication results are shown in Table 2.

3.6. Adverse events

Five trials had records of incidence number of adverse events. The analysis under random-effect model pooled estimate of RR was 0.99 (95% CI: 0.66, 1.48), which showed no significant difference between 2 groups ($P=.97$). The relevant details were showed in Fig. 8.

3.7. Subgroup analysis

Subgroup analysis was conducted according to the study design (multicenter or single-center). Six trials were multicenter trials, and the remaining 6 were single-center trials. In the multicenter studies, 87 out of 706 patients suffered PF with the octreotide prophylaxis, and 149 out of 698 patients suffered PF in the control group. There was a significant difference between the 2 groups in the induction of PF (RR = 0.58, 95% CI = 0.43–0.80, $P=.0008$). In the single-center subgroup, 50 out of 258 patients in the octreotide group had a PF postoperatively compared with 45 out of 240 in the control group. The pooled analysis under the random-effects model indicated that octreotide had no advantages in the prevention of postoperative PF (RR = 1.00, 95% CI = 0.77–1.32, $P=.98$). The results are discussed later. See Fig. 9.

Studies from different continents (Europe, America, or Asia) were also analyzed as subgroups: 8 studies from Europe, 2 from North America, and 2 from Asia. In the European subgroup, the pooled analysis indicated that octreotide had advantages in the prevention of postoperative PF (RR = 0.57, 95% CI = 0.43–0.76, $P<.0001$). In the American and Asian subgroups, there were no statistically significant differences in the prevention of postoperative PF between the 2 groups (RR = 1.26, 95% CI = 0.75–2.11, $P=.38$; RR = 0.87, 95% CI = 0.53–1.45, $P=.6$). See Fig. 10.

The 2 included studies stratified patients into 2 groups: high-risk and low-risk groups.[24,25] The subgroup meta-analysis of the low-risk and high-risk group patients had to be performed with available data regarding the total number of complications. The pooled analysis under random-effects in low-risk group with patient who suffered complications showed that there is no significant difference in the incidence of complications (RR = 0.58,

Table 1

Characteristics of studies included and clinical outcomes of the study population.

Authors, y	Multi or single center	Country	Study design	Groups (octreotide/control)	Age, y	Gender (M/F)	Intervention	PF	Mortality	Number of compli-cations	Pathology	Surgical approach
H. Friess et al, 1994	Multicenter	Germany	RCT	Octreotide 125 Control 121	51±9.33 52±10.00	92/33 82/39	100 μg, SC, every 8 h for 7d	22 46	4 7	82 126	Pancreatic cancer Periampullary cancer Endocrine tumor Chronic pancreatitis others	PD PPPD DPPHR Left resection Pancreaticojejunostomy et al
Marco Montorsi et al, 1994	Multicenter	Italy	RCT	Octreotide 111 Control 107	59.4±10.8 56.9±12.5	131/87	100 μg, SC, every 8 h for 7d	10 21	9 6	24 39	Pancreatic and periampullary cancer Chronic pancreatitis Endocrine tumor Miscellaneous others	PD PPPD DPPHR et al
P. Pederzoli et al, 1994	Multicenter	Germany	RCT	Octreotide 122 Control 130	52.6±1.1 53.6±1.2	78/44 75/55	100 μg, SC, every 8 h for 7d	11 24	2 5	19 38	Pancreatic adenocarcinoma Periampullary tumor Endocrine tumor Cystic tumor Chronic pancreatitis Others	PPPD DPPHR et al
H. Friess et al, 1995	Multicenter	Germany	RCT	Octreotide 122 Control 125	48±8.33 47±9.33	99/23 95/30	100 μg, SC, every 8 h for 8d	12 28	2 1	20 37	Chronic pancreatitis	PD PPPD DPPHR Left resection Pancreaticojejunostomy et al
Andrew M. Lowy et al, 1997	Single-center	American	RCT	Octreotide 57 Control 53	63 63	32/25 25/28	150 μg, SC, every 8 h for 5d	16 11	1 0	17 13	Pancreatic adenocarcinoma Periampullary adenocarcinoma Neuroendocrine carcinoma Other malignant tumors	PD
Charles J. Yeo et al, 2000	Multicenter	American	RCT	Octreotide 104 Control 107	63.9±1.3 65.5±1.1	59/45 52/55	250 μg, SC, every 8 h for 7d	11 10	1 0	42 36	Malignancy; chronic pancreatitis Other tumor	PD PPPD
Uwe J. Hesse et al, 2005	Single-center	Belgium	RCT	Octreotide 55 Control 50	59.93±12 58.98±13	42/13 35/15	100 μg, SC, every 8 h for 7d	5 4	1 0	6 6	Cancer Benign tumor Chronic pancreatitis	PD PPPD
O. Kollmar et al, 2008	Single-center	Switzerland	RCT	Octreotide 35 Control 32	59.9±2.0 64.8±2.0	24/11 17/15	100 μg, SC, every 8 h for 7d	3 1	1 0	14 10	Malignancy; Chronic pancreatitis Other tumor	PD PPPD

Authors, y	Multi or single center	Country	Study design	Groups (octreotide/control)	Age, y	Gender (M/F)	Intervention	PF	Mortality	Number of compli-cations	Pathology	Surgical approach
Bertrand Suc et al, 2004	Multicenter	France	RCT	Octreotide 122 Control 108	56 ± 14 57 ± 12	76/46 55/53	100 μg, SC, every 8 h for 10d	21 20	15 8	NA	Pancreatic, biliary, ampullar or duodenal tumor or chronic pancreatitis	PD PPPD
Kurumboor et al, 2012	Single-center	India	RCT	Octreotide 24 Control 21	NR	NR NR	100 μg, SC, every 8 h for 5d	18 16	NR NR	7 7	NR	PD
Fernandez et al, 2013	Single-center	Spain	RCT	Octreotide 32 Control 30	69 ± 13.25 69 ± 13.25	17/15 17/13	100 μg, SC, every 8 h for 10d	2 3	0 0	NR	Malignancy; Other tumor	PPPD
Kurumboor et al, 2015	Single-center	India	RCT	Octreotide 55 Control 54	58 ± 9.2 56 ± 11.6	31/24 35/19	100 μg every 8 h for 5 days	6 10	1 1	NR	Chronic pancreatitis	PD

DPPHR = duodenum-preserving pancreatic head resection, M/F = male/female, NR = not reported, PD = pancreaticoduodenectomy, PF = pancreatic fistula, PPPD = pylorus-preserving pancreaticoduodenectomy, RCT = randomized controlled trial, SC = subcutaneous.

Figure 2. Risk of bias summary: this risk of bias tool incorporated the assessment of randomization (sequence generation and allocation concealment), blinding (participants and outcome assessors), incomplete outcome data, selective outcome reporting, and other risks of bias. The items were judged as "low risk," "unclear risk," or "high risk." Red means "high risk," green means "low risk," and yellow means "unclear risk."

95% CI = 0.14–2.39, $P = .45$), while a significant difference in the incidence of complications in patients in high-risk group (RR = 0.61, 95% CI = 0.45–0.81, $P = .0006$). See Fig. 11.

3.8. Sensitivity analysis and publication bias

We performed a sensitivity analysis for assessing stability of pooled results. Among the most studies, the observed significant results were not obviously altered after sequentially omitting each study. In the pooled results comparing incidence of PF, after excluding the Fiess H study,[24] the heterogeneity decreased significantly (RR = 0.80, 95% CI = 0.61–1.05, $P = .11$, $I^2 = 38\%$), and showed that there is no significant different in preventing the

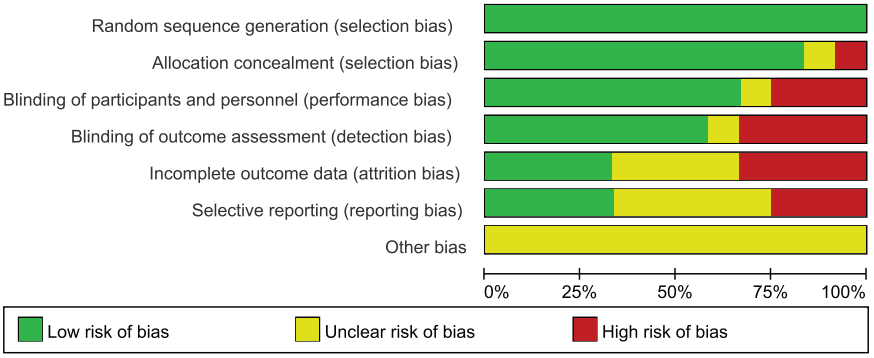

Figure 3. Risk of bias graph exhibiting the review of the authors' judgments about each risk of bias item, presented as percentages across all included studies.

incidence of PF between 2 groups. So it was regarded as a result of heterogeneity. Similarly, other 4 studies[23,25–27] were considered as the source of heterogeneity because the heterogeneity significantly changed and showed that there is no significant different in preventing the incidence of PF between 2 groups by excluding each of these studies in the pooled results comparing incidence of PF. Moreover, of the 12 studies evaluated, 6 studies used a double-blind method,[20,24–28] 1 adopted a single-blind method,[29] and 4 did not mention the blinding method.[18,21–23] One was a single-blind study[29] and 1 was an open-label trial.[19] Therefore, a sensitivity analysis was conducted to determine whether the exclusion of this study would change the result. Exclusion of this study from the meta-analysis did not substantially influence the results.

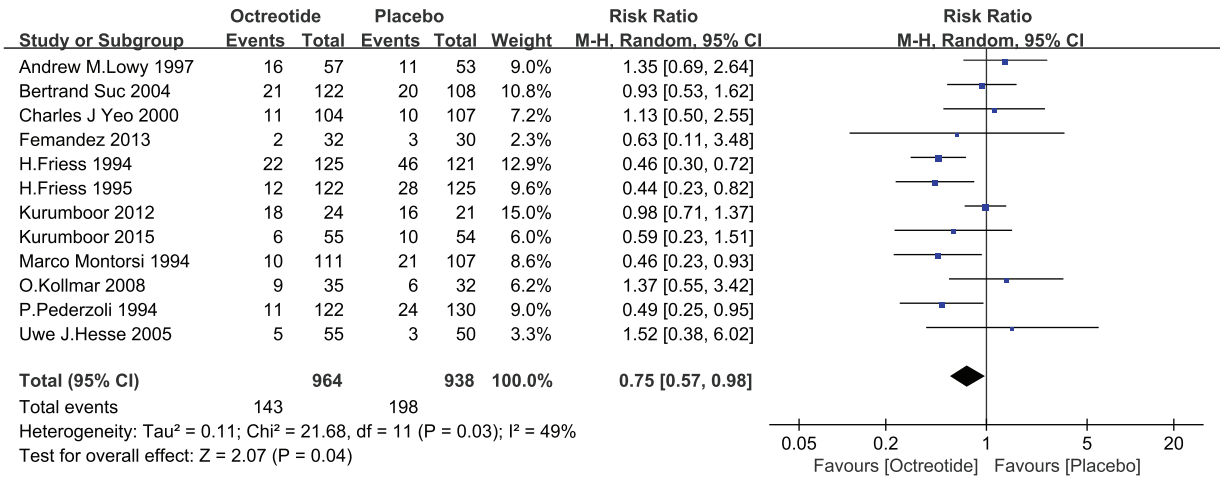

Figure 4. Forest plot of randomized controlled trials of prophylactic octreotide versus no intervention in pancreatic fistula. CI = confidence interval, RR = relative risk.

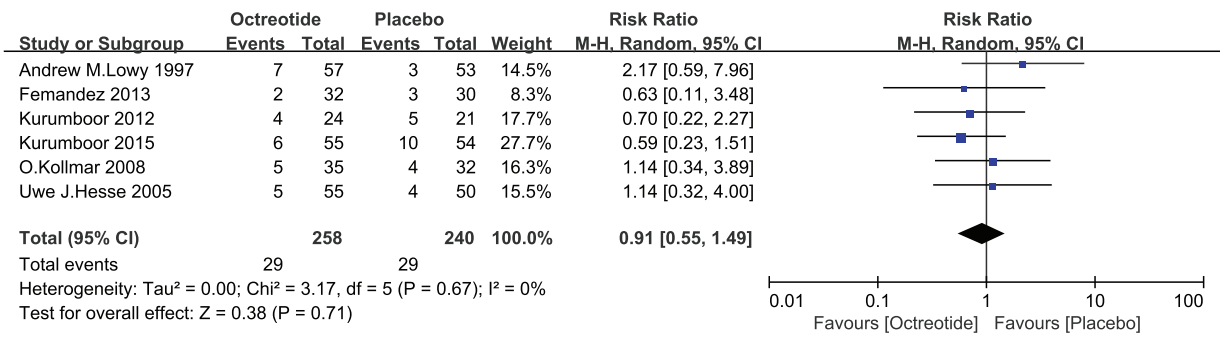

Figure 5. Forest plot of randomized controlled trials of prophylactic octreotide versus no intervention in clinically significant pancreatic fistula. CI = confidence interval, RR = relative risk.

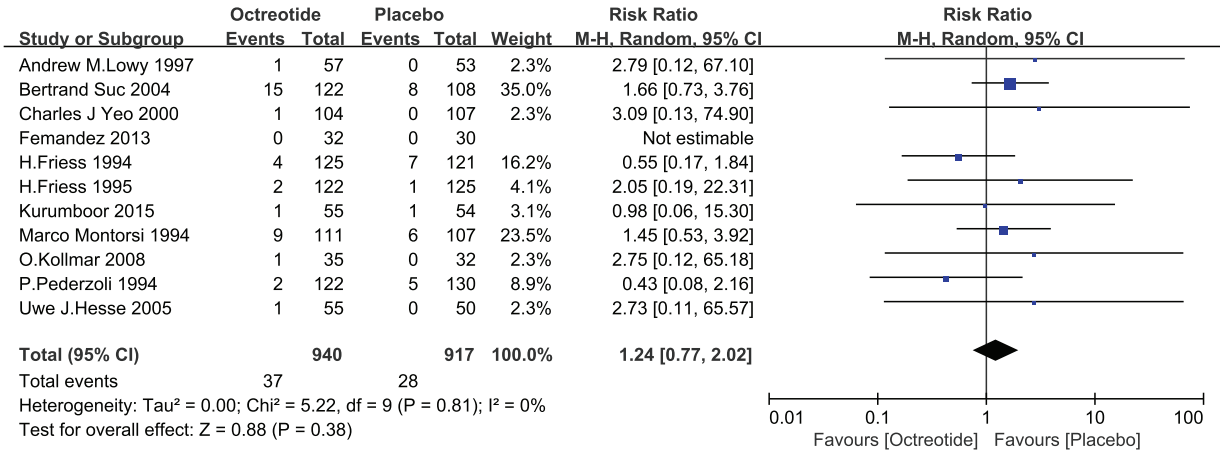

Figure 6. Forest plot of randomized controlled trials of prophylactic octreotide versus no intervention in mortality. CI = confidence interval, RR = relative risk.

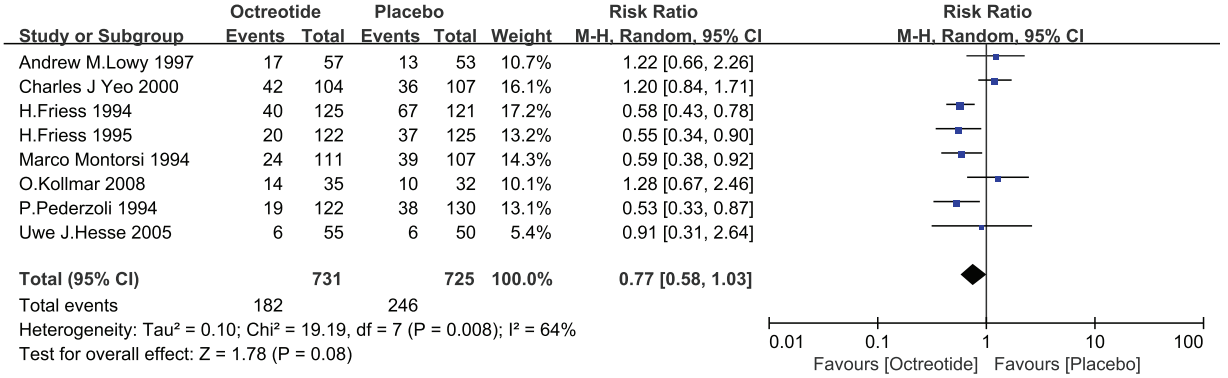

Figure 7. Forest plot of randomized controlled trials of octreotide versus no intervention in the incidence rate of complications. CI = confidence interval, RR = relative risk.

A funnel plot of randomized controlled trials reporting PF outcomes is shown in Fig. 12. Publication bias may exists, but was not apparent. The result was discussed later.

4. Discussion

4.1. Summary of the main results

PF remains the most frequent complication after pancreatic resection.[30] Some trials in the literature revealed that octreotide prophylaxis could significantly reduce the rate of PF.[24–27,31] However, several groups of investigators evaluated the octreotide prophylactic and reported no statistical benefit for patients who underwent pancreatic resection.[18,28,29,32,33] However, the results were quite conflicting.

This was an updated systematic review and meta-analysis of RCTs to assess the efficacy of octreotide prophylactic use for the prevention of complications after pancreatic resection. Octreotide could significantly reduce the rate of PF after resection.

Table 2

Results of complications of patients.

Complications	Number of including studies	Model	RR	95%CI	*P*	I^2%
Leakage of anastomosis	5	Random	0.94	0.56–1.60	0.83	27
Abscess	9	Random	0.84	0.61–1.15	0.28	0
Fluid collection	5	Random	0.61	0.42–0.89	0.01	0
Shock	3	Random	0.90	0.40–2.01	0.80	0
Sepsis	3	Random	0.48	0.17–1.32	0.15	12
Pulmonary insufficiency	9	Random	0.94	0.62–1.43	0.78	0
Renal insufficiency	4	Random	0.66	0.21–2.10	0.48	0
Bleeding	6	Random	1.08	0.66–1.77	0.76	0
Postoperative pancreatitis	6	Random	0.45	0.18–1.09	0.08	0
Wound infection	3	Random	0.86	0.52–1.41	0.55	0
Delayed gastric emptying	4	Random	0.80	0.46–1.38	0.42	0

CI = confidence interval, RR = risk ratio.

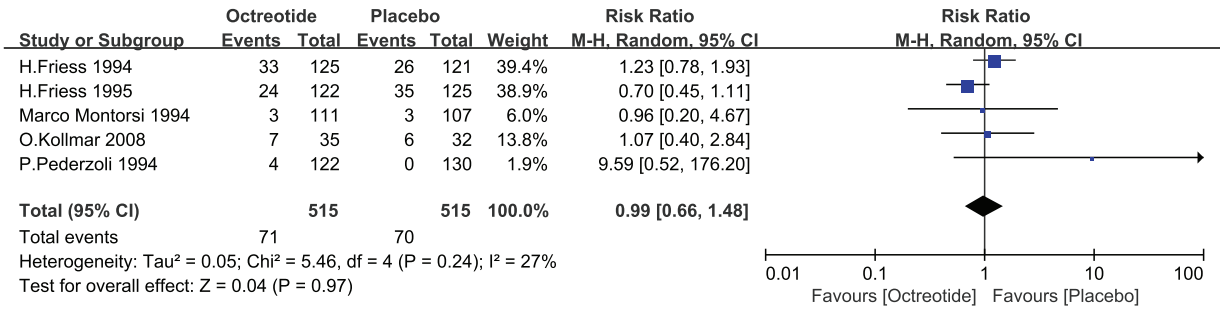

Figure 8. Forest plot of randomized controlled trials of the adverse effects to the study drugs (octreotide vs placebo). CI = confidence interval, RR = relative risk.

Additionally, the same findings were discovered in multicenter trials and the European subgroup by conducting subgroup analysis. Considering that 5 out of 6 trials, including multicenter RCTs, were from Europe, there is no doubt that similar results may be obtained. However, contradictory results were found in the remaining 6 single-center studies. These differences may be due to the experience level of the surgeon, the type of anastomosis, or the quality of the tissue. With the technical surgical improvements, the incidence of PF after PD has been successfully reduced.[34,35] The type of surgery could influence the rate of PF development.

The grading of PF with grades A, B, and C has gained widespread acceptance which were defined according to the clinical impact on patients hospital course.[36] Grade A postoperative pancreatic fistula was called a "biochemical leak," because it has no clinical importance. The analyses of overall occurrence of all grades PF (grades A, B, and C) and only to those having a clinical impact PF (only grades B and C) were conducted. In our study, 6 trials compared the use of octreotide and reported clinically significant PFs using the International Study Group of Pancreatic Fistula (ISGPF) definition while demonstrated no difference in the incidence of clinically significant PF with or without the use of drugs.[18–23] As for the result of clinically significant PF (grades B and C), there is no significant difference between octreotide and placebo groups. Considering that clinically significant PF may be closely related to the patient's surgical procedure, surgeon's technique, and the disease itself. Grade A postoperative pancreatic fistula is redefined and called a "biochemical leak," because it has no clinical importance and is no longer referred to a true pancreatic fistula in the 2016 update

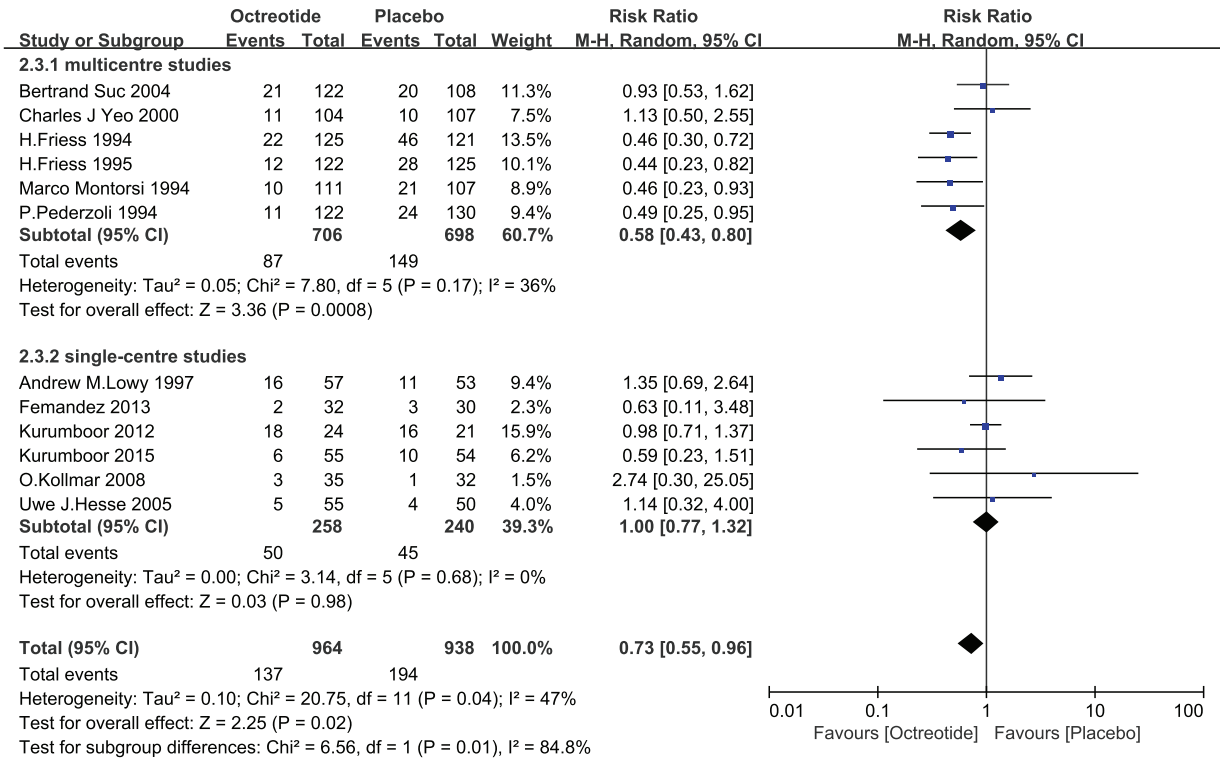

Figure 9. Forest plot of randomized controlled trials of octreotide versus no intervention with the type of study design (multicentre or singlecentre) in pancreatic fistula. CI = confidence interval, RR = relative risk.

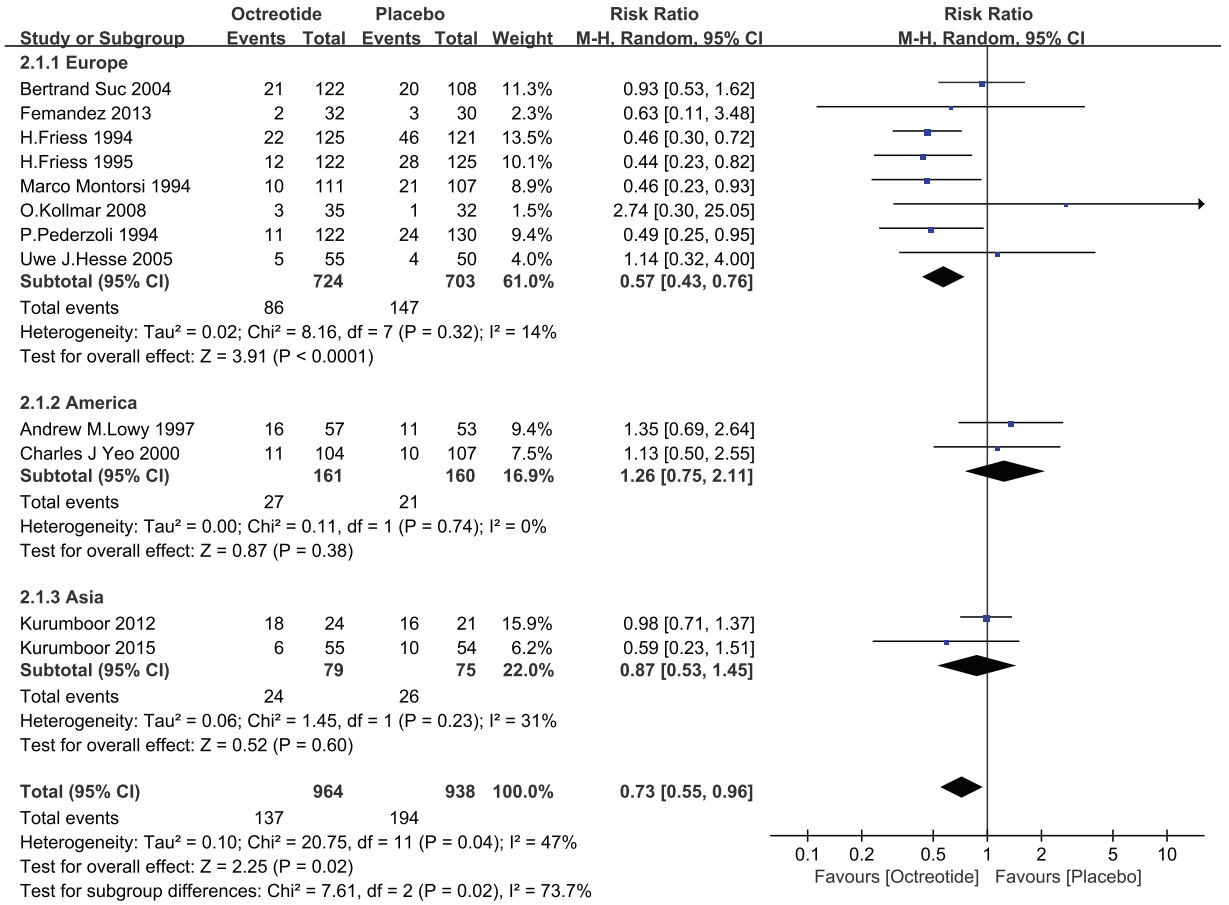

Figure 10. Forest plot of randomized controlled trials of octreotide versus no intervention with different continents (Europe or America or Asia) in pancreatic fistula. CI = confidence interval, RR = relative risk.

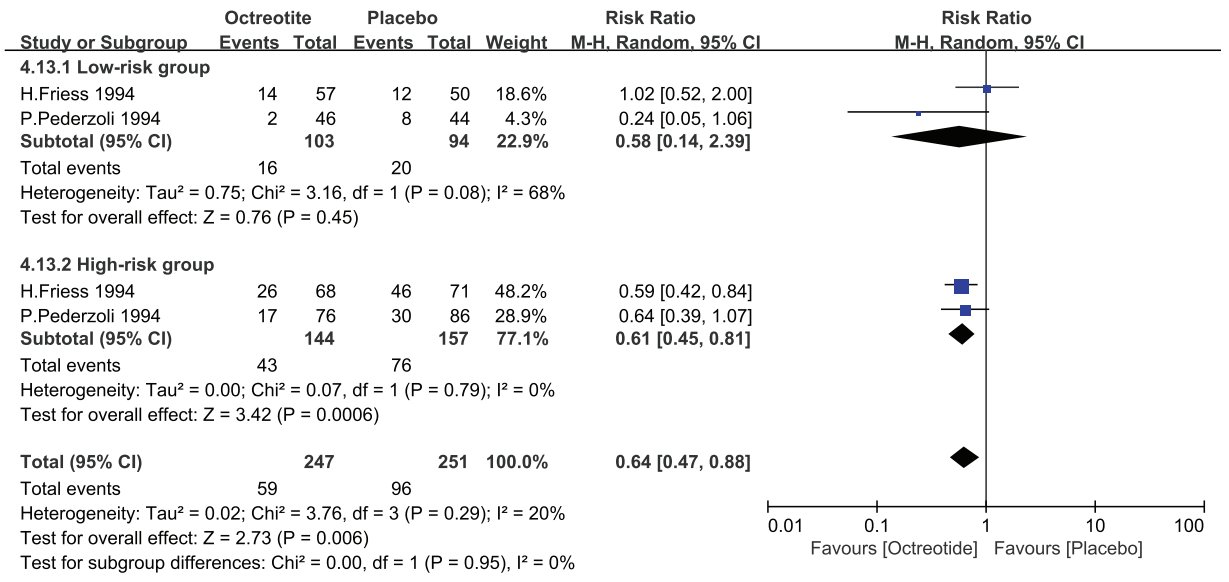

Figure 11. Forest plot of randomized controlled trials of octreotide vs. no intervention with the pathology of disease (low-risk and high-risk group) in the total number of patients with complications following pancreatic operation. CI = confidence interval, RR = relative risk.

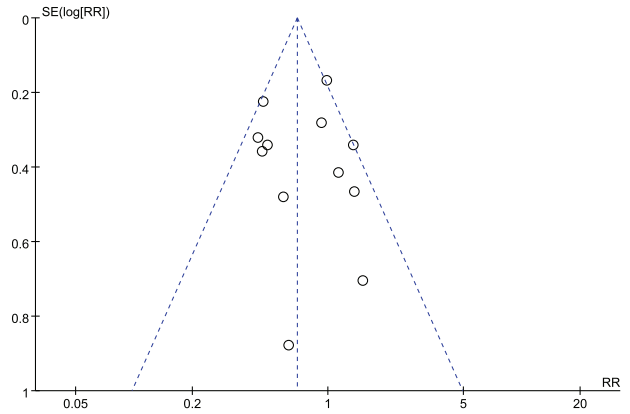

Figure 12. Funnel plots of randomized controlled trials of octreotide versus no intervention for outcome of pancreatic fistula. RR = risk ratio, SE = standard error.

of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula.[37] Therefore, we concluded that the occurrence of grade A PF is closely related to whether prophylactic use of octreotide is involved. In summary, our results support octreotide's benefit in avoiding the incidence of PF.

The definition of a PF varied in the 12 included studies and should be discussed. In this meta-analysis, we defined a PF as any volume with an amylase-rich fluid content of more than 3 times the serum level, exceeding 10 mL per 24 hours for more than 3 days. Fernandez et al[20] and Kurumboor et al[21] adopted the same definition, as did a trial in 1995.[27] However, Yeo et al[28] adopted a more conservative definition (>50 mL per 24 hours for more than 10 days or radiological pancreatic anastomosis disruption); this variation in definition may affect the results.

No significant difference in the rate of mortality was observed between the 2 groups. Although the 2 high-risk groups reached similar results, the *P* value was close to .05, and the horizontal block was located to the left of the vertical line. This result indicates a trend toward a decrease in mortality among patients suffering from pancreatic tumors. A study with a larger sample size would demonstrate the clinical implication of this difference.

An evaluation of the number of complications after pancreatic resection between the 2 groups revealed that there was no significant difference in the complication rate between the presence and absence of octreotide treatment. Studies by Friess et al[26] and Kurumboor et al[23] recruited only patients who suffered from chronic pancreatitis and indicated that octreotide had significant advantages in reducing the rate of complications. Thus, the pathology of pancreatic disease and the characteristics of the pancreatic parenchyma influence the incidence rate of complications.

As for the result of the adverse effects to the study drugs, there were no significant different between octreotide and placebo in induce adverse effects. A study reported that 59 patients (24 with octreotide, 35 with placebo) were observed which have side-effects during the study medication. Among these patients 43 patients (18 with octreotide, 25 with placebo) suffered some pain, burning or erythema at the injection site, and these effects did not require discontinuation of the treatment.[26] Other events such as nausea, vomiting, heartburn, diarrhoea, intestinal cramps, dysopia, and disturbance of coagulation. And these effects did not require discontinuation of the treatment as well. In Kollmar O study,[20] showed that 7 and 6 patients experienced delayed gastric emptying (DGE) with octreotide and placebo, respectively. This finding was not statistically significant. So, we speculated that DGE is one of surgical complications and may be not associated with the use of octreotide. The direct influence of surgical complications on DGE has been described in the previous studies.[38,39] In Montorsi M study,[27] 6 out of 218 patients experienced symptoms (nausea, vomiting, and diarrhea) possibly related to pharmacologic treatment (3 with octreotide, 3 with placebo). As well as the adverse events reported in other 3 including studies,[24,25,18] none of these symptoms necessitate discontinuation of the treatment.

4.2. Comparison with previous studies

Given the widespread application of octreotide, RCTs assessed its efficacy in preventing complications after pancreatic resection directly. A study by Closset et al[40] comparing somatostatin and octreotide proved that both somatostatin and octreotide have comparable efficacy in the prevention of complications after pancreatectomy. The function of octreotide in reducing fistula formation and promoting fistula closure is associated with 2 primary mechanisms: the inhibition of exocrine pancreatic secretion and the hardening of pancreatic tissue to facilitate safer anastomosis.[41] A meta-analysis performed by Alghamdi et al[42] summarized 7 RCTs and revealed that octreotide is associated with a significant reduction in the incidence of PF after pancreatic surgery, and no significant difference in postoperative mortality was observed. The results of the subgroup analysis according to the type of study design were consistent with our findings. A similar conclusion was also obtained by Li-Ling and Irving[43] and Gurusamy et al,[44] indicating that octreotide administration could reduce postoperative complications, particularly PFs, but could not reduce mortality. Different results have been summarized as well, showing that there is no decrease in the rate of PFs following octreotide administration after pancreatic resection.[15,16] One recently completed comprehensive review of the use of somatostatin analogs in the prevention of postoperative complications identified 15 RCTs involving 1352 patients and demonstrated that octreotide had no influence on the incidence of PF.[45] This study provided a relatively comprehensive evidence that prophylactic treatment with somatostatin or pasireotide have a potential role in reducing PF, while octreotide had no influence on the incidence of PF. As for the discrepancy between their and our findings, the potential clinical and methodological heterogeneity should be considered. The different search strategy and inclusion criteria may be attributed to the discrepancy. In Jin et al[45] study, a subgroup analysis of patients divided into low-risk and high-risk group (according to the different nature of pancreatic disease) cannot be performed because of limited data. However, in our study the subgroup analysis of patients in low-risk and high-risk group were available. In addition, 2 other subgroup analysis were conducted according to study design and geographical, which provided more comprehensive evidence about prophylactic use of octreotide have benefit to avoid PF. This is one advantages of our study. Comparing with Jin et al study which evaluated prophylactic somatostatin analogues (somatostatin, pasireotide, and octreotide) in PD, our study investigated the effect of prophylactic octreotide on postoperative complications such as PF, mortality, anastomosis leakage, abscess, fluid collection, shock, sepsis, pulmonary insufficiency and so on which may provide more comprehensive and targeted information in

evaluating the study drugs. According to the guidance of Cochrane Handbook, unpublished articles were involved in this meta-analysis what the previous article lacks may introduce publication bias. Rosenberg et al[46] suggested that compared with a placebo, octreotide is a dominant treatment strategy. The prophylactic use of octreotide is a cost-effective strategy for patients undergoing pancreatic resection, especially those patients who are at high-risk for developing complications. Because only double-blind, randomized, controlled clinical trials were recruited in this meta-analysis, the results were more reliable. Another cost-effectiveness comparison of octreotide and pasireotide prophylactics for the prevention of fistula after pancreatic surgery yielded a similar conclusion.[47]

To the best of our knowledge, this is an updated systematic review and meta-analysis designed to evaluate the prophylactic treatment of octreotide to prevent complications after pancreatic resection. To provide more evidence for clinical decision-making, this study incorporated updated RCTs with a more detailed subgroup analysis (i.e., different study designs, geographical locations, and disease pathologies) that assessed the main results of postoperative PF in addition to mortality and the total number of complications (i.e., anastomosis leakage, abscess, fluid collection, shock, sepsis, pulmonary insufficiency, renal insufficiency, bleeding, and postoperative pancreatitis) with the available data to assess the efficacy of octreotide in preventing complications after pancreatic resection. The lack of these assessments was a limitation of our previous report. Moreover, some different comprehensive results were also observed; these findings were compared with the latest meta-analysis. Our study included more RCTs and performed subgroup analyses based on the study design, geographical location, and disease pathology. And a funnel plot was made to reveal the publication bias.

4.3. Limitations of the study

Despite a comprehensive analysis, certain limitations of this meta-analysis should be discussed. First, the most important limitation is the scarcity of high-quality, multicenter, large-sample standard RCTs that directly assess the efficacy of octreotide. Second, the PFs in each study were assessed by different definitions, potentially inducing inevitable bias. Third, the occurrence of postoperative complications was related to many factors, such as operative technique, surgeon experience, tissue quality, hospital volume, total perenteral nutrition, and other medical therapies, making the database rather imprecise. Although funnel plot is still a widely used method to detect publication bias, it's limitations should be aware. For example, change of metrics would change the shape of the plot; true heterogeneity and poor methodological quality could also lead to an asymmetric plot.[48,49] Furthermore, Hozo algorithm was adopted for the parts of the included literature that did not directly provide means and SDs, which may have introduced bias. Moreover, different surgical procedures of pancreatic disease also affect the incidence of complications.[50] Clinical and methodological heterogeneity was seen in several parameters in the meta-analysis, given the variation in surgical techniques, patient composition, and preferences among different centers. Unfortunately, limited data are available on the cost and financial implications of octreotide use. In view of the heterogeneity, more large, high-quality clinical trials that evaluate the efficacy of octreotide should be conducted, and more detailed analyses, such as analyses of financial constraints and safety tolerance, should be performed to strengthen the reliability of these conclusions.

5. Conclusion

The prophylactic use of octreotide is recommended, particularly for the prevention of postoperative complications associated with pancreatic fistula and fluid collection as well as postoperative pancreatitis in patients undergoing pancreatic resection. However, no obvious differences were noted regarding mortality. Further studies are warranted to confirm the results of this meta-analysis and to define which patient subgroups may benefit the most from prophylactic octreotide administration.

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