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Pancreatic Duct Stents at Pancreaticoduodenectomy: A Meta-Analysis

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Key Words
Pancreatic duct stents · Pancreatoduodenectomy · Pancreaticojejunostomy · Meta-analysis · Trial sequential analysis

Abstract
Background and Objective: Several studies suggested that pancreatic stents had some benefit during pancreatoduodenectomy (PD), but others disagree. Whether pancreatic duct stents could prevent postoperative pancreatic fistula (POPF) is still under controversy. ***Methods:*** Randomized controlled trials published before November 2012 were all aggregated, focusing on the evaluation of pancreatic duct stents during PD. Trial data was reviewed and extracted independently by two reviewers. The quality of the including studies was assessed by the Cochrane handbook 5.1.0. ***Results:*** Seven studies were included, with a total of 793 patients. The results showed that compared with nonstents, stents during PD was associated with a significant difference on overall POPF rate (OR = 0.65, 95% CI 0.45–0.95, p = 0.02), POPF grades B and C (OR = 0.45, 95% CI 0.27–0.76, p = 0.003), and hospital stay (MD = –4.28, 95% CI –6.81, –1.75, p = 0.0009). Subgroup analyses showed that the external stent had a significant difference in the incidence of overall POPF (OR = 0.46, 95% CI 0.29–0.73, p = 0.0009), POPF grades B and C (OR = 0.49, 95% CI 0.30–0.79, p = 0.003), postoperative morbidity (OR = 0.63, 95% CI 0.42–0.96, p = 0.03), as well as hospital stay. ***Conclusions:*** Based upon this meta-analysis, there might be potential benefit in reducing POPF thanks to the use of pancreatic duct stents.

Introduction

As the standard resection for benign or malignant disease of the pancreatic head or periampullary region [1, 2], pancreatoduodenectomy (PD) is a complex surgical procedure, with a less than 5% operative mortality rate in specialized institutions around the world [1, 3–5]. Nevertheless, the surgical morbidity still remains high as 30–40% of the patients were suffering from one or more complications [6, 7], such as postoperative pancreatic fistula (POPF), intra-abdominal collection and delayed gastric emptying (DGE). POPF, one of the most common reported complications, occurs in 5–40% of the patients after PD [8–10], and is closely related to the increased morbidity and mortality seen after operations [11].

In the past decades, some techniques have been carried out to reduce POPF following PD, including somatosta-

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tin analogue octreotide, comparison of pancreaticogastrostomy versus pancreaticojejunostomy, and utilization of pancreatic duct stents. To date, the evidence from randomized controlled trials (RCTs) has not been able to expound whether the octreotide has specific effects on reducing POPF [8, 12–14], and the results of pancreaticogastrostomy versus pancreaticojejunostomy are also discordant [15–17]. After all, none of the above can completely eliminate the possibility of leakage.

The pancreatic duct stents, supporting tube drainage of the pancreatic stump, are usually inserted into the duct to make the pancreatic juice flow off directly after PD. However, confirming the published literature, we found that the conclusions were often under debate. So far, five meta-analyses [18–22] on this topic have been already performed to evaluate perioperative outcomes, but those conclusions might be not reliable enough for clinical decision-making as they are based on both RCTs and observational studies. There were not even any relatively indispensable interpretations of subgroup analysis or sensitivity analysis. Hence, it is necessary to carry out a new meta-analysis including RCTs only and to update the prior meta-analyses on the basis of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) items [23], as well as the GRADE system [24] used to grade the quality of overall evidence on outcome.

The aims of this study are to evaluate the effectiveness of pancreatic duct stents on postoperative outcomes following PD and to calculate the sample needed for this meta-analysis, hoping to provide much more reliable evidence for clinical decision-making and to guide further research.

Methods

Literature Search

We searched the following electronic databases: PubMed, EMBASE, ISI web of knowledge, the Cochrane library, Chinese Biomedical Literature Database (CBM), Chinese Journal Full-text Database (CNKI), Chinese science and technology periodicals database (VIP) and the WanFang database; it was completed in November 2012. All published and unpublished RCTs were searched without any language restriction.

The search items were as follows: stent, stents, stenting, anastomosis, pancreatic resection, internal, external, in situ, ex situ, pancreatoduodenectomy, pancreaticojejunostomy, pancreaticogatrostomy, Whipple, pancreatic fistula, leakage, PF, POPF, pancreatic anastomosis, etc. using Medical Subject Headings terms combined with free text terms.

We also performed a supplementary literature search through *Google Scholar* and some heading journals, such as *Annals of Surgery* and *Archives of Surgery*, from 1990 to at least November 2012. All search strategies were determined after numerous presearches.

Study Selection

Endnote X5 software was used for removing the duplicates. After two reviewers independently screened the titles and abstracts of the initially identified literature, reviews, comments, letters and case reports were excluded, as well as those observational studies through reading the full text. Finally, the eligible trials were identified. Disagreements were resolved through discussions. As some studies were performed by the same institutions or the same authors from one trial, we took the one with high quality or the latest publication into the data analysis.

Data Extraction

Two reviewers independently extracted the following data: titles, years of publication, country and districts, years of study, study design, interventions, stent materials, definitions of POPF, number of patients (age, sex, BMI, etc.), usage of octreotide, methodological quality, etc.

Primary outcome: POPF (overall POPF and POPF grades B and C).

Secondary outcomes: postoperative morbidity, overall mortality, DGE, intra-abdominal collections, time of hospital stay.

The criteria and definitions of all these outcomes above are shown in table 1. When studies overlapped or were duplicated, we extracted the data with the longest follow-up.

Criteria for Inclusion and Exclusion

We included these studies into the meta-analysis if they met all three of the following inclusion criteria: (1) RCTs irrespective of blinding used or not; (2) pancreatic duct stents for pancreatic resections, and (3) patients suffering from PD due to benign or malignant disease of the pancreatic head or periampullary region and had to undergo operative placement of stents.

The following were the exclusion criteria: (1) studies conducted in children (less than 18 years of age), and (2) PD due to acute pancreatitis or injury of the pancreas.

Assessment of Methodological Quality of Including Studies

We assessed the risk of bias of these including studies on the basis of the Cochrane Collaboration Handbook [25]. The quality items assessed were sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. We recorded problems in respect of these issues in full, and for individual studies each of the criteria was assigned a label of 'yes', 'unclear' or 'no' to estimate the risk of bias. Each study was subjected to quality assessment by two reviewers. Discrepancies were resolved by discussion.

Using GRADEpro (http://ims.cochrane.org/revman/other-resources/gradepro, version 3.6) [26] for all outcomes, the results were shown in a summary of findings (SoF) table which was provided by the Cochrane collaboration [27]. RCTs are regarded as high-quality evidence unless they are limited by serious defects to bias due to the impact on study quality, inconsistency, indirectness, imprecise or sparse data, or high probability of reporting bias [28]. If any of the items mentioned above existed, the rating quality of evidence grade and grading strength recommendations could be downgraded to moderate, low or very low [29].

Table 1. Criteria on all outcomes

Included studies	Primary outcome POPF	Secondary outcomes				
		morbidity	mortality	delayed gastric emptying	intra-abdominal collection	hospital stay
Kuroki et al. [38]	ISGPF	NA	NA	NA	NA	NA
Motoi et al. [2]	ISGPF	postoperative complications	hospital mortality	unclear	unclear	postoperative hospital stay
Pessaux et al. [39]	ISGPF	complications occurring within 30 days after surgery or hospital stay	death occurring within 30 days after surgery or hospital stay	Clavien's classification	Clavien's classification	postoperative hospital stay
Poon et al. [40]	≥10 ml/day (3 times serum level) more than 3d after surgery	postoperative complications	hospital mortality	delayed gastric emptying >7 days	unclear	postoperative hospital stay
Winter et al. [42]	ISGPF and JHH	Clavien's classification	postoperative all-cause death	Clavien's classification	Clavien's classification	postoperative hospital stay
Kamoda et al. [37]	ISGPF and JHH	postoperative complications	postoperative all-cause death	unclear	unclear	postoperative hospital stay
Tani et al. [41]	ISGPF	postoperative complications	postoperative all-cause death	ISGPS	ISGPS	postoperative hospital stay

ISGPF = International Study Group on Pancreas Fistula definition; JHH = Johns Hopkins Hospital local definitions; ISGPS = International Study Group on Pancreas Surgery; Clavien's classification = see ref. [44]; NA = no assessment this outcome in full-text; unclear = no description according to any definition used in full text.

Statistical Methods

This meta-analysis was performed in accordance with the recommendations of the PRISMA statements [23]. Both direct and indirect comparisons were performed if necessary.

The statistical analysis was performed and the forest plots were generated via the Review Manager (version 5.2.0) software application [30]. The OR was calculated along with its 95% CI for dichotomous outcomes and mean difference (MD) was calculated for continuous outcomes. Statistical heterogeneity among studies was assessed by means of χ^2 and the extent of inconsistency was assessed by the I^2 statistic [31]. The random-effects model and the fixed-effect model were used. If I^2 was less than 50% (cut-off point), we used the fixed-effect model, while if I^2 was more than 50%, we chose the random effects model. A rough guide to the interpretations of I^2 from the Cochrane Collaboration Handbook [25] regards 0–40% as heterogeneity might not be important, 30–60% as moderate heterogeneity, and 75–100% as considerable heterogeneity. Descriptive techniques were used when clinical heterogeneity existed or when no data could be used in pooling analysis. The stability of outcomes was tested by sensitivity analysis if necessary.

ITC software (http://www.cadth.ca/en/resources/about-this-guide/download-software, version 2.0) was used when indirect comparison was needed. This analysis was possible for the same placebo-controlled trials. Adjusted indirect comparison of pooled estimates was then performed according to the study of Song et al. [32]. The random effect was also conducted and weights OR was used in the effect measure. If both direct and indirect comparisons were available in the systematic reviews of randomized trials, the analytical method described above has been shown to produce results that are 93% concordant with the results of direct comparisons [32]. Indirect comparison was conducted to support our conclusion towards primary outcome (POPF) only if direct comparison could only provide weak evidence due to lack of RCTs and small sample size.

Trial sequential analysis (TSA) was performed to reduce the risk of random errors. TSA is a tool for quantifying the statistical reliability of the data in a cumulative meta-analysis [33], controlling alpha and beta values for sparse data, and for repetitive testing on accumulating data [34]. It is also a methodology that combines a required information size calculation (cumulated sample sizes of included trials) with the threshold of statistical significance. In order to control for the risks of random errors due to sparse data and multiplicity, TSA was performed for the dichotomous outcomes [35]. We adapted a relative risk reduction of 20%, an alpha (type I error) of 5%, a beta (type II error) of 20%, and the diversity of the meta-analysis [36]. It was just used for the primary outcome (i.e. POPF); also, it was possible to approximate how many patients should be randomized in the next trial to make the meta-analysis cross either of the monitoring boundaries and the futility boundaries.

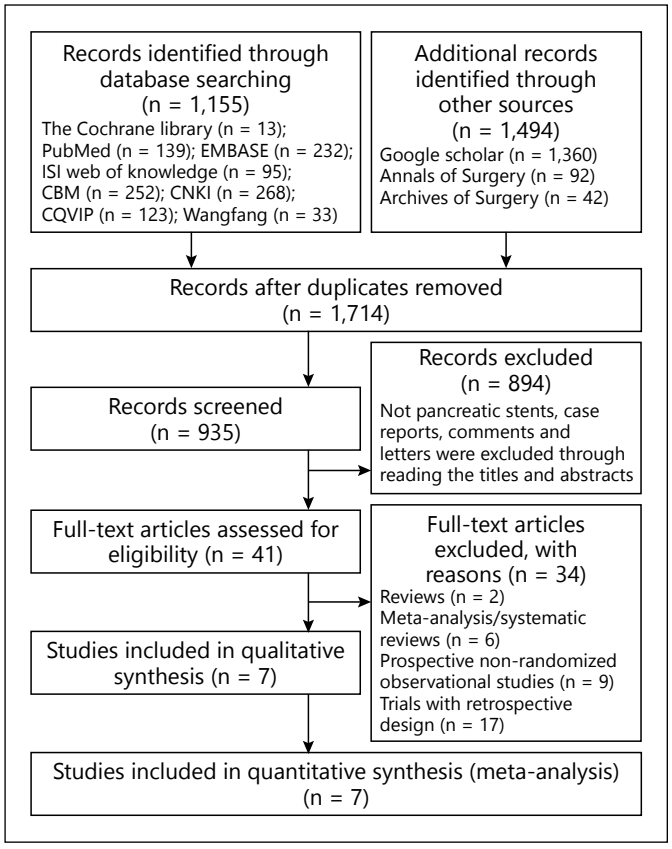

Fig. 1. PRISMA 2009 flow diagram.

Results

Selected Studies

Our initial search strategies yielded 2,649 potential articles, and there were 935 records after removing the duplicates, 41 of which were selected through scanning titles and abstracts. By a detailed full-text read, seven RCTs [2, 37–42] were ultimately identified in 793 patients. Figure 1 shows the PRISMA statement of the search flow in detail.

Study Characteristics

The included studies were published between 2006 and 2012. Four [2, 37, 38, 41] of them were conducted in Japan, and three studies took place in Hong Kong [40], France [39] and the USA [42]. The interventions of the four studies [2, 38–40] were comparisons between external duct stent and nonstent, and two studies [37, 41] compared external with internal stents. Only one group [42] studied the effect of the internal stent. More of the study characteristics are showed in table 2.

Results of Methodological Quality

All have used random allocation sequences, and the exact methods of randomization were clear in four trials [2, 39, 41, 42]. Six trials [2, 37, 39–42] had adequate allocation concealment with a blind envelope, except for one trial [38]. Two trials [2, 40] reported that opening of the envelope was performed during the operation by a third person who was not involved in the procedure after the resection was completed and immediately before pancreaticojejunostomy anastomosis, so we considered that they had lower risks of error. Others were considered to have high risks in blinding participants and personnel. The blinding of the statistician was unclear in all of the studies.

Results of the Meta-Analyses

A summary of these meta-analyses is shown in table 3.

Stents versus Nonstents

POPF. Five trials [2, 38–40, 42] compared stents with nonstents ($P_{heterogeneity}$ = 0.07, I^2 = 50%), and the fixed model was used. The result showed that there was a significant difference in the incidence of POPF (OR = 0.65, 95% CI 0.45–0.95, p = 0.02). While POPF grades B and C based on ISGPF criteria [43] were merged, the result also showed that it had a benefit on POPF (OR = 0.45, 95% CI 0.27–0.76, p = 0.003). According to the SoF table of the GRADE, the quality of the current evidence was low due to the inherent methodological property of the surgery trials in which was difficult to perform blinding except for blinding of the statistician. Allocation concealment was unclear in 60% of the included studies, as well as the significant unexplained heterogeneity among these identified studies. Also, the result of TSA showed that although there was a difference between the two groups (Z-curve has crossed the Z-score of ±1.96), the Z-curve did not cross the monitoring boundary and the risk of false-positive probably did exist. More patients (at least 1,160) will be needed in the future to confirm this conclusion (fig. 2).

Postoperative Morbidity. Four trials [2, 39, 40, 42] reported on postoperative morbidity ($P_{heterogeneity}$ = 0.26, I^2 = 25%) using a fixed model, and current evidence shows that there was no difference in the incidence of postoperative morbidity (OR = 0.75, 95% CI 0.54–1.04, p = 0.08). According to the GRADE system, the quality of evidence of postoperative morbidity was moderate due to the high risk of blinding, and allocation concealment was also unclear in 50% of the included studies.

Table 2. Characteristics of the studies

Including studies	Years of studies	Country/ district	Number of cases	Median age, years	Gender (male, %)	Interventions	Stent materials	Surgical technique	Octreotide/ somatostatin	Pancreas texture (soft/hard)	Pancreatic duct	BMI	Surgeons' management
Kuroki et al. [38]	2006.05–2009.10	Japan	45	68.1+11.2 68.2+8.4	56.5 54.5	EXS vs. NS	5 Fr diameter pancreatic drainage tube	ES-DM-PJ	NA	23/0 22/0	NA NA	21.0±2.8 21.9±3.0	single-center, the surgeons' administration was not given
Motoi et al. [2]	2007.12–2012.04	Japan	93	66.0 (33–79) 66.5 (32–80)	55.3 63.0	EXS vs. NS	5 Fr polyvinyl catheter	ES-DM-PJ	no	24/23 23/23	21/26 20/26	21.7 (14.3–32.4) 21.5 (16.3–29.3)	single center, a team of specialized surgeons, with a single surgeon performing PJ in all patients
Pessaux et al. [39]	2006.01–2009.03	France	158	60.8+11.8 60.6+11.8	50.6 58.0	EXS vs. NS	3–6 Fr polyvinyl catheter	ES-DM-PJ/ ES-DM-PG	yes	77/0 81/0	77/0 81/0	24.6±4.0 25.2±4.7	multicenter, specialized surgeons, the techniques were chosen by individuals
Poon et al. [40]	2000.06–2006.10	Hong Kong	120	61+12 62+13	51.7 68.3	EXS vs. NS	3–8 Fr polyvinyl catheter	ES-DM-PJ	no	33/27 33/27	NA NA	NA NA	single-center, a team of specialized surgeons, the techniques were chosen by individuals
Winter et al. [42]	2004.01–2005.11	USA	234	67 (33–68) 63 (27–89)	58.3 54.6	INS vs. NS	3.5–8 Fr plastic pediatric feeding tube	ES-DM-PJ/ EE-IN-PJ	no	57/0, 0/58 56/0, 0/63	NA NA	NA NA	single-center, 90% surgical procedures were performed by two surgeons from all nine
Kamoda et al. [37]	2003.01–2007.01	Japan	43	9/13 (≥65/<65) 14/7 (≥65/<65)	36.4 33.3	EXS vs. INS	5 Fr catheter	ES-DM-PJ/ EE-IN-PJ	no	13/9 12/9	NA NA	NA NA	single-center, all surgical procedures were performed by three senior surgeons
Tani et al. [41]	2005.04–2007.08	Japan	100	70 (44–87) 68 25–84)	56.0 54.0	EXS vs. INS	5 Fr polyethylene pancreatic drainage	ES-DM-PJ	no	15/35 22/28	NA NA	NA NA	single-center, the surgeons' administration was not given

EXS = External pancreatic duct stent; INS = internal pancreatic duct stent; NS = nonstent; ES = end-to-side; EE = end-to-end; DM = duct-to-mucosa; IN = invagination; PJ = pancreaticojejunostomy; PG = pancreaticogastrostomy; NA = no assessment.

Table 3. The summary of the meta-analyses

Outcome	Number of studies	Experiment		Control		Heterogeneity		Effect estimate	
		events	total	events	total	p	I^2, %	OR/MD (95% CI)	p
Stents vs. nonstents (experiment: stents; control: nonstent)									
POPF	5 [2, 34–36, 38]	70	322	95	328	0.07	50	0.65 [0.45, 0.95]	0.02
POPF (grades B and C)	4 [2, 34–36]	29	207	54	209	0.41	0	0.45 [0.27, 0.76]	0.003
Postoperative morbidity	4 [2, 35, 36, 38]	144	299	169	306	0.26	25	0.75 [0.54, 1.04]	0.08
Overall mortality	4 [2, 35, 36, 38]	7	299	10	306	0.66	0	0.73 [0.28, 1.88]	0.51
Delayed gastric emptying*	4 [2, 35, 36, 38]	33	299	45	306	0.03	66	0.80 [0.32, 2.01]	0.63
Intra-abdominal collections	4 [2, 35, 36, 38]	23	299	24	306	0.64	0	0.97 [0.53, 1.77]	0.93
Time of hospital stay	2 [35, 36]	–	137	–	141	0.22	35	–4.28 [–6.81, –1.75]	0.0009
External stent vs. nonstent (experiment: external stents; control: nonstent)									
POPF	4 [2, 34–36]	39	207	69	209	0.70	0	0.46 [0.29, 0.73]	0.0009
POPF (grades B and C)	4 [2, 34–36]	35	207	61	209	0.67	0	0.49 [0.30, 0.79]	0.003
Postoperative morbidity	3 [2, 35, 36]	78	184	100	187	0.31	15	0.63 [0.42, 0.96]	0.03
Overall mortality	3 [2, 35, 36]	5	184	6	187	0.51	0	0.86 [0.27, 2.73]	0.80
Delayed gastric emptying*	3 [2, 35, 36]	17	184	30	187	0.03	71	0.71 [0.19, 2.69]	0.62
Intra-abdominal collections	3 [2, 35, 36]	15	184	18	187	0.58	0	0.82 [0.40, 1.70]	0.60
Time of hospital stay	2 [35, 36]	–	137	–	141	0.22	35	–4.28 [–6.81, –1.75]	0.0009
Internal stent vs. nonstent (experiment: internal stents; control: nonstent)									
POPF	1 [38]	31	115	26	119	–	–	1.32 [0.73, 2.40]	0.36
Postoperative morbidity	1 [38]	66	115	69	119	–	–	0.98 [0.58, 1.64]	0.93
Overall mortality	1 [38]	2	115	4	119	–	–	0.51 [0.09, 2.83]	0.44
Delayed gastric emptying	1 [38]	16	115	15	119	–	–	1.12 [0.53, 2.39]	0.77
Intra-abdominal collections	1 [38]	8	115	6	119	–	–	1.41 [0.47, 4.19]	0.54
External stent vs. internal stent (experiment: external stents; control: internal stents)									
POPF	2 [37, 41]	18	72	20	71	0.55	0	0.84 [0.40, 1.78]	0.65
POPF (grades B and C)	2 [37, 41]	5	72	4	71	0.65	0	1.25 [0.32, 4.85]	0.75
Postoperative morbidity	2 [37, 41]	41	72	32	71	0.69	0	1.61 [0.83, 3.14]	0.16
Overall mortality	2 [37, 41]	1	72	0	71	–	–	3.06 [0.12, 76.95]	0.50
Delayed gastric emptying	2 [37, 41]	6	72	5	71	0.64	0	1.20 [0.35, 4.13]	0.77
Intra-abdominal collections	2 [37, 41]	5	72	5	71	0.58	0	0.99 [0.29, 3.40]	0.99

* Random models were used.

Overall Mortality. Four trials [2, 39, 40, 42] reported on overall mortality ($P_{heterogeneity}$ = 0.66, I^2 = 0%) using a fixed model. Comparing with nonstents, the stents had no benefit on the incidence of overall mortality (OR = 0.73, 95% CI 0.28–1.88, p = 0.51). According to the SoF table of the GRADE, the quality of this outcome was low on account of the high risk of blinding, as well as the small sample size and number of events provided. Additionally, the 95% CI around the pooled effect was wide.

Delayed Gastric Emptying. Four trials [2, 39, 40, 42] reported DGE ($P_{heterogeneity}$ = 0.03, I^2 = 66%), two studies of which [39, 42] used Clavien's classification [44]. Then the random model was used and the result showed that there was no difference on the rate of DGE (OR = 0.80, 95% CI 0.32–2.01, p = 0.63). The SoF table of the GRADE showed that the quality on DGE was moderate due to the high risk of blinding.

Intra-Abdominal Collections. Four trials [2, 39, 40, 42] reported on intra-abdominal collection ($P_{heterogeneity}$ = 0.64, I^2 = 0%), two of which [39, 42] used Clavien's classification [44] carried out on a fixed model. There was no difference between the stents and nonstents (OR = 0.97,

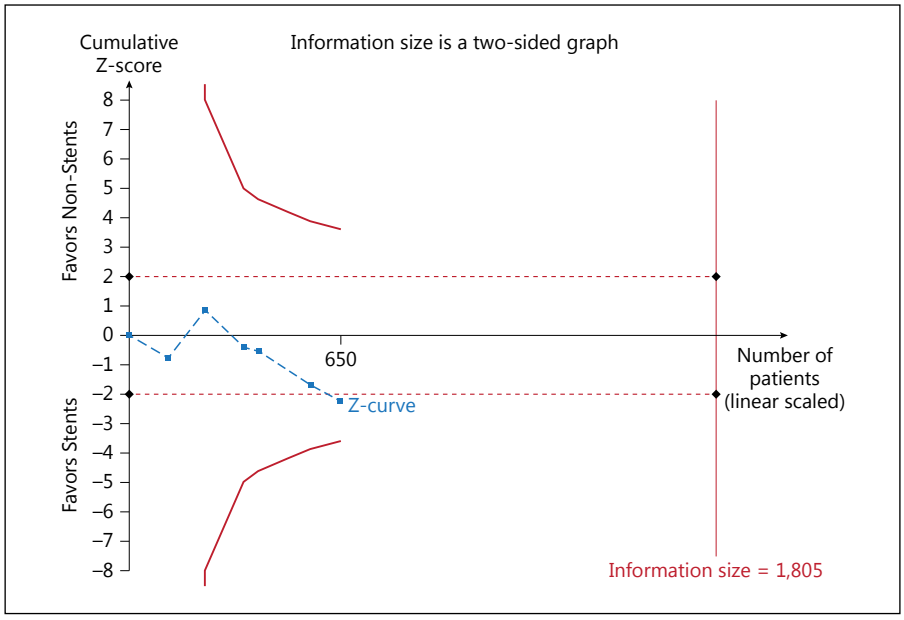

Fig. 2. Trial sequential analysis on POPF. The red line is the trial sequential analysis monitor boundary according to a relative risk reduction of 20%, type I error of 5% and type II error of 20%. The red horizontal line is the Z-score of ±1.96, equal to two-sided p = 0.05. X-axis = Number of patients randomized; Y-axis = Z-score. TSA on POPF of 5 RCTs (marked with black dots) illustrates that the cumulative Z-curve did not cross the monitoring boundary. The required information size was calculated to 1,805 (the vertical line).

95% CI 0.53–1.77, p = 0.93). From the SoF, we considered that the quality of intra-abdominal collections was moderate due to the high risk of blinding of the participants and personnel in the studies.

Time of Hospital Stay. Four trials [2, 39, 40, 42] reported on hospital stay, mainly focusing on the postoperative hospital stay. Motoi et al. [2] found that there was no significant difference in the hospital stay (p = 0.614), and Winter et al. [42] also drew a similar conclusion, though no p value was reported. However, the available data pooled from two studies [39, 40] showed that stent (external) had benefits in the hospital stay when it was compared with nonstent (MD = –4.28, 95% CI –6.81, –1.75, p = 0.0009). We considered that the result of quality on hospital stay was moderate.

Subgroup Analysis

External Stent versus Nonstent. The results showed that comparing with nonstent, we found that the external pancreatic duct stent made a significant difference in the incidence of overall POPF (fixed model, OR = 0.46, 95% CI 0.29–0.73, p = 0.0009), as well as POPF grades B and C (fixed model, OR = 0.49, 95% CI 0.30–0.79, p = 0.003). Meanwhile, it also had a benefit on postoperative morbidity (fixed model, OR = 0.63, 95% CI 0.42–0.96, p = 0.03) and hospital stay (fixed model, MD = –4.28, 95% CI –6.81, –1.75, p = 0.0009). However, the difference was not proven on overall mortality (fixed model, OR = 0.86, 95% CI 0.27–2.73, p = 0.80), DGE (random model, OR = 0.71, 95% CI 0.19–2.69, p = 0.62), or intra-abdominal collection (fixed model, OR = 0.82, 95% CI 0.40–1.70, p = 0.60). According to the SoF table, the quality of the currently available evidence on all outcomes was moderate except for DGE. The main reason for downgrading was still the possibility of the high risk resulting from blinding, which was difficult to perform owing to the inherent methodological property of the surgery trials. Besides, the quality on DGE was low because of the significantly unexplained heterogeneity among the included studies.

Internal Stent versus Nonstent. Only one study [42] compared internal stent with nonstent. The result did not show any benefit of POPF, postoperative morbidity, overall mortality, DGE, intra-abdominal collections, or hospital stay (p > 0.05). Indirect comparison between the internal stent and nonstent was performed regarding POPF. The result also showed no effects in preventing POPF (OR = 0.55, 95% CI 0.23–1.32). According to the SoF table of the GRADE, the quality of the available evidence was very low, and the reasons for downgrading contained a high risk of blinding, use of both direct and indirect comparison, and the fact that only one study had been included.

External versus Internal Stent

Two trials [37, 41] compared external with internal stent. The meta-analysis results showed that the rate of POPF was not statistically different (OR = 0.84, 95% CI

0.40–1.78, p = 0.65), nor did POPF grades B and C (OR = 1.25, 95% CI 0.32–4.85, p = 0.75), postoperative morbidity (OR = 1.61, 95% CI 0.83–3.14, p = 0.16), overall mortality (OR = 3.06, 95% CI 0.12–76.95, p = 0.50), DGE (OR = 1.20, 95% CI 0.35–4.13, p = 0.77), or intra-abdnominal collection (OR = 0.99, 95% CI 0.29–3.40, p = 0.99) show any significant differences. Hospital stay was reported in two studies: Tani et al. [41] reported a significant difference between the two groups (p = 0.016), while Kamoda et al. [37] showed no significant difference without providing any p values. According to the SoF table, the quality of the current evidence on all outcomes was low. We considered that the reasons for downgrading were as follows: high risk of blinding, small sample size, number of events, and wide 95% CI of the pooled effect.

Discussion

In this meta-analysis, the results indicated that the pancreatic duct stent had a potential benefit in reducing the rate of POPF but moderate heterogeneity existed ($P_{heterogeneity}$ = 0.07, I^2 = 50%). It reminded us that the statistics were unstable and called for more well-designed studies. The evidence from observational studies in a previous meta-analysis [18] also supported that the pancreatic duct stent had advantages in reducing the POPF, with a significance of p < 0.001. Based on the ISGPF definition [43], POPF grades B and C was a matter of concern. The results proved that its usage was associated with a statistically significant difference. Also, it could shorten the hospital stay (days) after PD. The TSA results showed that the Z-curve did not cross the monitoring boundary and that the risk of false-positives still exists. More patients (at least 1,160) are needed to be included in future studies. Differences in other outcomes, such as postoperative morbidity, overall mortality, DGE and intra-abdominal collection, were not found. Subgroup analyses showed that compared with nonstent, the external stent had advantages in the incidence of POPF and postoperative morbidity, as well as postoperative hospital stay. Meanwhile, the current weak evidence from only one RCT [42] prompted us to believe that the advantage of an internal stent was not apparent. Also, indirect comparison also showed that it had no advantages in preventing POPF. So, further research, especially randomized trials on the internal duct stent, is required. As far as comparison between the external and internal stent was concerned, the results displayed that pancreaticojejunostomy with an internal stent was also an effective and alternative treatment following PD, but we considered it insufficiently reliable to make a clinical decision because only two studies were included. According to the SoF table of GRADE, the quality of the currently available clinical evidence was from moderate to low.

Some interpretations, supporting the results above, should be recognized. Because of the occurrence of less gastrointestinal motility in the early days after PD, a great deal of pancreatic juice or bile accumulates around the jejunal loop of the anastomosis. The stents, supporting tube drainage of the pancreatic stump, were usually built into the pancreatic duct to allow a smooth outflow of the pancreatic juice after PD, ease corrosion by pancreatic juice, and to avoid pancreatitis due to blocking of the pancreatic duct stent related to postoperative anastomotic edema. The pancreatic duct stent called for a more precise placement of sutures during pancreatic anastomosis.

Several risk factors, including the soft texture of the pancreas and a nondilated pancreatic duct [2, 37, 39–42] as well as BMI [2], have been identified as important in the development of POPF. Of the included studies, Winter et al. [42] reported a higher POPF rate with the use of an internal stent in the setting of soft pancreatic texture (internal stent 47.4% vs. nonstent 33.9%) but no difference was seen (p > 0.05). Kuroki et al. [38] also reported that there was no significant difference on POPF in the setting of soft pancreas as assessed by MRI (external stent 21.7% vs. nonstent 27.2%). However, a significant difference on POPF (external stent 21.7% vs. nonstent 27.2%) was concluded by Pessaux et al. [39]. Tani et al. [41] demonstrated that there were no differences in the incidence of overall POPF and POPF grades B and C (overall: external stent 26.7% vs. internal stent 45.5%; grades B and C: external stent 13.3% vs. internal stent 13.6%). On the other hand, with anastomosis between pancreatic duct and jejunum mucous being adapted by more and more surgeons, it was considered a beneficial method to reduce the rate of POPF [45]. Some surgeons held the view that the pancreatic juice could not contact the operational residual end, so it was not necessary because the POPF could be avoided, and that the effect of the pancreatic duct stents would be replaced by pancreaticojejunostomy using duct-to-mucosa anastomosis [46]. However, the present meta-analysis showed a potential advantage in pooled outcomes towards the POPF.

As for the limitations, the results of the present study should be interpreted with a level of caution because the number of RCTs included was probably too small to support firm conclusions. Also, the surgical experience and

volume would have an impact on the outcomes. Another limitation was that a potential publication bias might exist among the including studies.

Conclusion

Current evidence demonstrates that there was a trend to reduce the POPF through using pancreatic duct stents. Meanwhile, currently available data prompted that both external and internal stents were alternative treatments following PD. However, it needs to be confirmed using more patients and this study might provide information for further research.

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Disclosure Statement

The authors declare no conflicts of interest.

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