Pancreatogastrostomy vs pancreatojejunostomy after pancreaticoduodenectomy: An updated meta-analysis of RCTs and our experience

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Abstract

BACKGROUND
Pancreatoduodenectomy (PD) is one of the most important operations in hepatobiliary and pancreatic surgery.

AIM
To evaluate the advantages and disadvantages of pancreaticojejunoanostomy (PJ) and pancreatogastrostomy (PG).

METHODS
This meta-analysis was performed using Review Manager 5.3. All clinical randomized controlled trials, in which patients underwent PD with pancreatico-digestive tract reconstruction via PJ or PG, were included.

RESULTS
The search of PubMed, Wanfang Data, EMBASE, and the Cochrane Library provided 125 citations. After further analysis, 11 trials were included from nine counties. In all, 909 patients underwent PG and 856 underwent PJ. Meta-analysis showed that pancreatic fistula (PF) was a significantly lower morbidity in the PG group than in the PJ group (odds ratio [OR] = 0.67, 95% confidence interval [CI]: 0.53-0.86, P = 0.002); however, grades B and C PF was not significantly different between the two groups (OR = 0.61, 95% CI: 0.34-1.09, P = 0.09). Postoperative hemorrhage showed a significantly lower morbidity in the PJ group than in the PG group (OR = 1.47, 95% CI: 1.05-2.06, P = 0.03). Delayed gastric emptying was not significantly different between the two groups (OR = 1.09, 95% CI: 0.83-1.41, P = 0.54).

CONCLUSION
There is no difference in the incidence of grades B and C PF between the two groups.
groups. However, postoperative bleeding is significantly higher in PG than in PJ. Binding PJ or binding PG is a safe and secure technique according to our decades of experience.

**Key words:** Pancreaticojejunostomy; Pancreaticogastrostomy; Systematic review; Meta-analysis

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**Core tip:** Pancreatico-digestive tract anastomosis after pancreaticoduodenectomy is still controversial. This systematic review and meta-analysis aimed to further evaluate the role and importance of pancreaticojejunostomy and pancreaticogastrostomy. We compared the complications of these two surgical procedures, including pancreatic fistula, delayed gastric emptying, and hemorrhage.

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**INTRODUCTION**

Pancreatoduodenectomy (PD) is the main treatment procedure for benign and malignant tumors of the pancreatic head, lower common bile duct, and ampulla[1]. The incidence of complications after PD is still high, with some large pancreatic centers reporting an incidence of approximately 10-45%. The incidence of pancreatic fistula (PF), delayed gastric emptying (DGE), and gastrointestinal or abdominal hemorrhage has been reported to be 3-45%, 5%-61%, and 1%-8%, respectively. Other complications include abdominal empyema, incision infection, and pulmonary infection[2].

Since the establishment of PD, pancreatico-digestive tract reconstruction has been a highly valued research area, which is considered to be closely related to the success/failure of the surgery[3]. In general, pancreatico-digestive tract reconstruction includes pancreaticojejunostomy (PJ) and pancreaticogastrostomy (PG). Unlike gastrointestinal anastomosis, these two types of reconstruction after pancreatic surgery are diverse, with different results and evaluations. Therefore, there is still room for improvement in PJ and PG, and these procedures are still the focus of future research in PD.

This systematic review and meta-analysis aimed to further evaluate the role and importance of pancreatico-digestive tract anastomosis. Further, the advantages and disadvantages of PJ and PG were compared to provide a valuable reference for a more reasonable and safe choice of pancreatico-digestive tract reconstruction in the future.

**MATERIALS AND METHODS**

**Eligibility criteria**

All clinical randomized controlled trials, in which patients underwent PD with pancreatico-digestive tract reconstruction via PJ or PG, were included.

**Information sources**

Studies were identified by searching electronic databases and scanning reference lists of articles. No limits were applied for languages and foreign papers were translated to English. The search was applied to Medline, Wanfang Data, EMBASE, Science Citation Index Expanded, and the Cochrane Library. The last search was run on March 15, 2019.

**Search**

We used the following search terms to search all trial registers and databases: Pancreatoduodenectomy or Pancreatoduodenectomies or Duodenopancreatectomy or
Duodenopancreatectomies or Pancreaticoduodenectomy or Whipple or PD or Whipple procedure or Pancreatoduodenal resection or Pancreaticoduodenal resection, Pancreaticojunostomy or Pancreaticojejunostomies or Pancreatojejunostomy or Pancreatojejunal anastomosis or Pancreatojejunal anastomosis or Pancreateoenteric anastomosis or Pancreateojejunal anastomosis or Pancreatojejunostomy or Pancreaticoduodenectomy or Whipple procedure or Pancreaticoduodenal resection.

Study selection
Eligibility assessment was performed independently in an unblinded standardized manner by two reviewers. Disagreements between reviewers were resolved by discussion.

Data collection process
One review author extracted the following data from the included studies and the second author checked the extracted data. Disagreements were resolved by discussion between the two review authors; if no agreement could be reached, a third author would take the decision.

Data items
Data were extracted from each included trial on: (1) Characteristics of trial participants including age, disease, and number of patients; (2) Intervention with PG vs PJ; (3) Type of outcome measures including the definition and occurrence of PF, DGE, and other postoperative complications.

Risk of bias in individual studies
To ascertain the validity of eligible randomized trials, two independent reviewers with adequate reliability determined the adequacy of randomization, concealment of allocation, blinding of patients, healthcare providers, data collectors, and outcome assessors.

Statistical analysis
The meta-analysis was performed using Review Manager 5.3. The Chi-square test was used to test heterogeneity among studies. The heterogeneity level was judged according to $I^2$. Relative risk (RR), weighted mean difference (WMD), standardized mean difference (SMD), and 95%CI (confidence interval) were used.

For data with clinical heterogeneity, it is not easy to merge effect quantities. First, we tested heterogeneity among studies. Then subgroup analysis or meta-regression analysis was conducted according to heterogeneity. If data were insufficient or heterogeneity cannot be found, a random-effects model was used. The homogeneity of data was tested by the $\chi^2$ test, and the homogeneity was quantitatively analyzed by the $I^2$ test. If there was no statistical heterogeneity, a fixed-effects model was used. When statistical analysis showed heterogeneity, a random-effects model was used. The significance level of the hypothesis test was set at $P < 0.05$.

To assess the risk of bias across studies, we plotted the effect by the inverse of its standard error for each trial. The symmetry was assessed both visually, and formally by the Egger’s test.

RESULTS
A total of 11 studies involving 11 trials were identified for inclusion in the review[14-24]. The search of PubMed, Wanfang Data, Embase, and the Cochrane Library provided 125 citations. Of the total 125 citations, 29 studies were discarded because they did not meet the inclusion criteria. Nine additional studies were discarded because full texts for these were not available. The full texts of the remaining 65 citations were examined in further detail. Following this, 51 studies were found not to meet the inclusion criteria as described, and three were repeat studies from the same institute at different time points (we chose the latest study in this case). Finally, 11 studies met the inclusion criteria and were included in the systematic review. Figure 1 shows the flow diagram of study selection (Figure 1).

From 1995 to 2016, 11 trials were included from nine counties. In all, 909 patients underwent PG and 856 underwent PJ. PF was defined and classified following the International Study Group on Pancreatic Fistula (ISGPF) consensus guidelines in seven trials[15,17-22] (Table 1). The quality of these 11 trials is presented in Figure 2.

PF data were available for all 11 trials randomizing 1765 patients and reporting data for them. In the meta-analysis, there was no significant heterogeneity between these studies ($I^2 = 20\%$); therefore, a fixed-effects model was applied. PF showed a significantly lower morbidity in the PG group than in the PJ group (odds ratio [OR] =
DISCUSSION

PF is one of the most common complications after PD. PF not only causes serious complications such as abdominal bleeding but also increases the length of hospital stay and cost for patients. Our study showed that PG anastomosis can reduce the incidence of all grades of PF than PJ anastomosis. In 2005, the ISGPF defined PF and divided it into three levels\(^\text{[25]}\). In 2016, the group adjusted the classification of PF and defined grade A PF as a biochemical fistula\(^\text{[8]}\). Therefore, in this study, we considered the incidence of grades B/C PF in subgroup analysis. We believe that this statistical analysis has more clinical value and significance. We found no statistical difference in grades B/C PF between the two groups (OR = 1.09, 95% CI: 0.83-1.41, \(P = 0.54\)) (Figure 6).

Nine trials including 780 PG and 738 PJ patients were included for the analysis of DGE. In the meta-analysis, there was no significant heterogeneity between these studies (\(I^2 = 47\%\)), and therefore a fixed-effects model was applied. DGE was not significantly different between the two groups (OR = 1.09, 95% CI: 0.83-1.41, \(P = 0.54\)) (Figure 6).

**Figure 1 Study flow diagram.**

0.67, 95% CI: 0.53-0.86, \(P = 0.002\)) (Figure 3). Grade A PF did not affect the disease outcome; therefore, we further analyzed the incidence of grades B and C PF. Seven trials with 603 PG and 581 PJ patients were included. In the meta-analysis, there was a significant difference in heterogeneity between these studies (\(I^2 = 61\%\)); accordingly, a random-effects model was applied. Grades B and C PF was not significantly different between the two groups (OR = 0.61, 95% CI: 0.34-1.09, \(P = 0.09\)) (Figure 4).

Nine trials with 788 PG and 734 PJ patients were included for analyzing postoperative hemorrhage. In the meta-analysis, there was no significant heterogeneity between these studies (\(I^2 = 0\%\)); accordingly, a fixed-effects model was applied. Postoperative hemorrhage showed a significantly lower morbidity in the PJ group than in the PG group (OR = 1.47, 95% CI: 1.05-2.06, \(P = 0.03\)) (Figure 5).

 Nine trials including 780 PG and 738 PJ patients were included for the analysis of DGE. In the meta-analysis, there was no significant heterogeneity between these studies (\(I^2 = 47\%\)), and therefore a fixed-effects model was applied. DGE was not significantly different between the two groups (OR = 1.09, 95% CI: 0.83-1.41, \(P = 0.54\)) (Figure 6).
Table 1  Characteristic of included trials

| Author          | Year | Country      | Study type                                           | Number of PG | Number of PJ | Definition of PF                                                                 |
|-----------------|------|--------------|-----------------------------------------------------|--------------|--------------|----------------------------------------------------------------------------------|
| Yeo et al[14]   | 1995 | United States| Single blind, controlled randomized, single center trial | 73           | 72           | PF was defined as drainage of greater than 50 mL of amylase-rid fluid on or after postoperative day 10 |
| Duffas et al[23]| 2005 | France       | Single blind, controlled randomized, multicenter trial | 81           | 68           | Fluid obtained through drains or percutaneous aspiration, containing at least 4 times normal serum values of amylase for 3 day |
| Bassi et al[25] | 2005 | Italy        | Single blind, controlled randomized, single center trial | 69           | 82           | Any clinically significant output of fluid, rich in amylase, confirmed by fistulography |
| Bassi et al[8]  | 2008 | Spain        | Single blind, controlled randomized, single center trial | 53           | 55           | ISGPF definition                                                                |
| Wellner et al[13]| 2012 | Germany      | Single blind, controlled randomized, single center trial | 59           | 57           | ISGPF definition                                                                |
| Wang et al[9]   | 2012 | China        | Single blind, controlled randomized, multicenter trial  | 83           | 53           | ISGPF definition                                                                |
| El Nakeeb et al[20] | 2013 | Egypt        | Single blind, controlled randomized, single center trial | 45           | 45           | ISGPF definition                                                                |
| Topal et al[18] | 2013 | Belgium      | Single blind, controlled randomized, single center trial | 162          | 167          | ISGPF definition                                                                |
| Figueras et al[22] | 2013 | Spain        | Single blind, controlled randomized, multicenter trial  | 65           | 58           | ISGPF definition                                                                |
| Greendar et al[24] | 2015 | Canada       | Single blind, controlled randomized, single center trial | 48           | 50           | Either radiologically proven anastomotic leak or continued drainage (via drain, enterocutaneous fistula, or wound) of lipase-rich fluid on postoperative day 10 |
| Keck et al[19]  | 2016 | Germany      | Single blind, controlled randomized, multicenter trial  | 171          | 149          | ISGPF definition                                                                |

PG: Pancreaticogastrostomy; PJ: Pancreaticojejunostomy; PF: Postoperative pancreatic fistula.

anastomotic site, thus preventing the leakage of pancreatic juice from the pinholes, to fundamentally eliminate the possibility of PF. At present, BPJ has been applied in more than a thousand of cases, which has a significant effect on the prevention of PF after surgery[7]. In 2010, Buc, a French scholar, named BPJ procedure as Peng’s PJ and reported that BPJ was a safe and secure technique[28]. In 2008, Peng created the binding pancreaticogastrostomy (BPG), which simplified the operation steps of the previous pancreas-stomach anastomosis[29]. After continuous improvement, only the bundled method was used in the posterior wall of the stomach, avoiding the suture of pancreas parenchyma and thus greatly shortening the surgical time and preventing anasto-
Figure 2  Quality of the included trials.

motic leakage. BPG not only solves the problem of excessive pancreatic stump but also reduces the harm of bile leakage because the biliary-jejunal anastomosis is not in the same channel as PG anastomosis[27]. The mid-term results of the randomized controlled study showed that the incidence of PF in BPG and BPJ was acceptable[17].

In recent years, with the continuous development of laparoscopic technology, laparoscopic PD has gradually become an alternative method, used as a routine treatment in some pancreatic surgeries[30-32]. Thus, laparoscopic pancreatico-gastrointestinal anastomosis has become a new focus for research. Owing to the limitation of the laparoscopic visual field, pancreatic duct to mucosa anastomosis is the first choice of procedure under laparoscopy[30].

The attempt of various methods makes the technique of PJ dazzling. However, the basic content cannot be separated from pancreas-jejunal (stomach) anastomosis or pancreatic duct-jejunal (stomach) anastomosis. The objective of evaluation should be as simple as possible. Moreover, the lower the incidence of pancreatic leakage compared with classical anastomosis, the better. As long as these principles are followed, sample enlargement and randomized controlled trials should be conducted...
Figure 3  Forest plot of the incidence of all grades of postoperative pancreatic fistula. PG: Pancreaticogastrostomy; PJ: Pancreaticojejunostomy; PF: Postoperative pancreatic fistula.

to find the best method.
### Figure 4
Forest plot of the incidence of grade B/C postoperative pancreatic fistula. PG: Pancreaticogastrostomy; PJ: Pancreaticojejunostomy; PF: Postoperative pancreatic fistula.

| Study or subgroup | PG Events | Total | PJ Events | Total | Weight | M-H, fixed, 95%CI | Odd ratio |
|-------------------|-----------|-------|-----------|-------|--------|------------------|-----------|
| El Nakeeb A 2013  | 7 45      | 45    | 2 53      | 55    | 1.11%  | 1.89 [0.51, 6.97] |           |
| Fernandez-Cruz L 2008 | 7 65   | 65    | 1 65      | 66    | 6.9%   | 0.18 [0.04, 0.85] |           |
| Figueras J 2013   | 7 65      | 65    | 1 65      | 66    | 15.0%  | 0.25 [0.10, 0.65] |           |
| Grendar J 2015    | 8 48      | 48    | 1 48      | 49    | 12.8%  | 1.47 [0.47, 4.59] |           |
| Keck T 2016       | 34 71     | 71    | 3 74      | 77    | 20.8%  | 0.87 [0.51, 1.50] |           |
| Topal B 2013      | 13 62     | 62    | 1 63      | 64    | 18.8%  | 0.35 [0.18, 0.70] |           |
| Wellner UF 2012   | 6 59      | 59    | 1 59      | 60    | 12.6%  | 0.81 [0.25, 2.57] |           |
| **Subtotal (95%CI)** | **603** | **581** | **100.0%** | 20.0% | 0.61 [0.34, 1.09] | |           |
| Total events      |            |       | 77        | 112   |        |                  |           |
| Heterogeneity: Tau² = 0.34; Chi² = 15.33, df = 6 (P = 0.02); I² = 61% |
| Test for overall effect: Z = 1.67 (P = 0.09) |
| Test for subgroup differences: Not applicable |

### Figure 5
Forest plot of the incidence of postoperative hemorrhage. PG: Pancreaticogastrostomy; PJ: Pancreaticojejunostomy.

| Study or subgroup | PG Events | Total | PJ Events | Total | Weight | M-H, fixed, 95%CI | Odd ratio |
|-------------------|-----------|-------|-----------|-------|--------|------------------|-----------|
| Bassi C 2005      | 3 69      | 69    | 1 69      | 70    | 9.3%   | 0.58 [0.14, 2.39] |           |
| Cheung 2012       | 3 83      | 83    | 1 84      | 85    | 4.2%   | 0.96 [0.15, 5.92] |           |
| Duffas JP 2005    | 13 81     | 81    | 1 82      | 83    | 14.6%  | 1.25 [0.50, 3.14] |           |
| El Nakeeb A 2013  | 1 45      | 45    | 2 47      | 49    | 1.7%   | 1.00 [0.06, 16.50] |           |
| Fernandez-Cruz L 2008 | 1 53   | 53    | 2 55      | 57    | 1.7%   | 1.04 [0.06, 17.04] |           |
| Figueras J 2013   | 13 65     | 65    | 1 66      | 67    | 10.5%  | 1.82 [0.67, 4.93] |           |
| Keck T 2016       | 36 171    | 171   | 1 172     | 173   | 25.5%  | 2.07 [1.11, 3.87] |           |
| Topal B 2013      | 21 162    | 162   | 1 163     | 164   | 25.9%  | 1.31 [0.67, 2.59] |           |
| Wellner UF 2012   | 6 59      | 59    | 1 60      | 61    | 6.5%   | 1.50 [0.40, 5.62] |           |
| **Total (95%CI)** | **788** | **734** | **100.0%** | 100.0% | **1.47 [1.05, 2.06]** | |           |
| Total events      |            |       | 97        | 64    |        |                  |           |
| Heterogeneity: Chi² = 3.56, df = 8 (P = 0.89); I² = 0% |
| Test for overall effect: Z = 2.23 (P = 0.03) |
Figure 6  Forest plot of the incidence of delayed gastric emptying. PG: Pancreaticogastrostomy; PJ: Pancreaticojejunostomy; PF: Postoperative pancreatic fistula.

ARTICLE HIGHLIGHTS

Research background
Pancreatoduodenectomy (PD) is one of the most important operations in hepatobiliary and pancreatic surgery. Pancreatico-digestive tract reconstruction includes pancreaticojejunostomy (PJ) and pancreaticogastrostomy (PG). Unlike gastrointestinal anastomosis, these two types of reconstruction after pancreatic surgery are diverse, with different results and evaluations. Therefore, there is still room for improvement in PJ and PG, and these procedures are still the focus of future research in PD.

Research motivation and objectives
This systematic and meta-analysis aimed to evaluate the role and importance of pancreatico-digestive tract anastomosis. Advantages and disadvantages of PJ and PG were compared to provide a valuable reference and safe choice in the future.

Research methods
This search was applied to Medline, Wanfang Data, Embase, Science Citation Index Expanded, and the Cochrane Library. The last search was run on March 15, 2019. All clinical randomized controlled trials, in which patients underwent PD with pancreatico-digestive tract reconstruction via PJ or PG, were included. The Chi-square test was used to test heterogeneity among studies. The heterogeneity level was judged according to $I^2$, relative risk (RR), weighted mean difference (WMD), standardized mean difference (SMD), and 95%CI were used.

Research results
In the meta-analysis of postoperative hemorrhage, there was no significant heterogeneity between these studies ($I^2 = 0$%); accordingly, a fixed-effect model was applied. Postoperative hemorrhage showed a significantly lower morbidity in the PJ group than in the PG group (OR = 1.47, 95%CI: 0.48-4.49, $P = 0.03$). In the meta-analysis of DGE, there was no significant heterogeneity between these studies ($I^2 = 47$%), and therefore a fixed-effects model was applied. DGE was not significantly different between the two groups (OR = 1.09, 95%CI: 0.83-1.41, $P = 0.54$).

Research conclusions
Our group has studied the anastomosis of the pancreas and digestive tract for more than 20 years, and has accumulated some experiences. We established the binding pancreaticojejunostomy (BPF) and binding pancreaticogastrostomy (BPG). The mid-term results of the randomized controlled study showed that the incidence of PF in BPG and BPF was acceptable.

Research perspectives
Laparoscopic pancreaticogastrointestinal anastomosis has become a new focus for research. The objective of evaluation should be as simple as possible. Moreover, the lower the incidence of pancreatic leakage compared with classical anastomosis, the better. As long as these principles are followed, sample enlargement and randomized controlled trials should be conducted to find the best method.
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