Review Article
Pancreatic duct stenting on postoperative pancreatic fistula: a systematic review and network meta-analysis

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Abstract: Background: The strategy of transanastomotic pancreatic ductal stenting is always classified into two types (internal and external stenting), but whether stenting would be appropriate and which is more appropriate for transanastomotic drainage remains debatable. We performed a network meta-analysis to evaluate external, internal and no transanastomotic pancreatic ductal stenting on decreasing incidence of pancreatic fistula (PF) and other adverse events following pancreaticoduodenectomy. Methods: We conducted a literature search to identify relevant available articles published without language restriction from EMBASE Databases, PubMed and the Cochrane Library. Studies comparing outcomes of external, internal and no stents placement in pancreaticoduodenectomy were eligible for inclusion. Results: Eight randomized controlled trials (n=1530 patients) published were included in this network meta-analysis. We found out that internal stenting (OR=1.4, 95% CrI=0.78, 2.7) and no stenting (OR=1.7, 95% CrI=0.85, 3.7) did not show a higher incidence of PF, delayed gastric emptying rate, morbidity and mortality than external stenting. However, the ranking probability analysis showed external stenting had the lowest probabilities of being ranked first in almost all four comparisons (1.6% for pancreatic fistula, 8.6% for DGE, 8.4% for morbidity and 23.5% for mortality). Conclusions: The current meta-analysis suggests that internal and no stenting appears to be the same effective as external stenting for patients undergoing pancreaticoduodenectomy in terms of postoperative pancreatic fistula, delayed gastric emptying rate, morbidity and mortality.

Keywords: Pancreatic duct stent, pancreatic fistula, pancreaticoduodenectomy, network meta-analysis

Introduction
Pancreaticoduodenectomy (PD), as the optimum treatment for resectable pancreas carcinoma and peripancreatic neoplasms, has been well performed for years. Recently, the advances of preoperative management and surgical skills lead to a new dimension to the treatment of patients undergoing PD, and mortality of PD has been less of 5% in many specialized institutions [1-3]. However morbidity following PD is still very high (30-50% in high-volume centers) [4]. One of the major complications is pancreatic fistula (PF) due to unsatisfactory pancreatico-jejunal anastomosis. The frequency of PF has a larger variation range of 2.5%-50% resulted from different techniques and limited proficiency of anastomosis [5-8]. And other complications following PF, such as intra-abdominal abscess, intra-abdominal hemorrhage may account for mortality [9, 10].

There have not been sufficiently effective strategies to prevent PF after PD, whereas substantial pharmacological interventions (such as somatostatin analogues) and surgical techniques which include anastomosis techniques (duct-to-mucosa anastomosis or invagination technique) and pancreatic duct reconstruction methods were designed to decrease the rate of PF [11-13]. Recently several studies indicated that PF could be avoided by the placement of transanastomotic pancreatic ductal stents which diverted pancreatic juice away from anastomosis site to protect the pancreatico-jejunal anastomosis from the decomposition of pancreatic enzymes [14, 15]. The strategy of transanastomotic pancreatic ductal stenting is
always classified into two types (internal and external stenting), but whether stenting would be appropriate and which is more appropriate of two types of stenting for transanastomotic drainage remains suboptimal when the debates on external versus internal stenting, external versus no stenting and internal versus no stenting have been conducted in several studies [14, 16]. The comparison between external and internal stenting or no stenting in previous meta-analysis had several limitations regarding small sample of randomized controlled trials and absence of subgroup analysis on PF in terms of different ISGPF grade, as well as statistical heterogeneity due to pooling of results from RCTs and OCS [13, 17]. Therefore we evaluated external, internal and no transanastomotic pancreatic ductal stenting on decreasing incidence of PF and other adverse events following PD, in the way of network meta-analysis, with only RCTs.

Materials and methods

Search strategy

We conducted a literature search to identify relevant available articles published without language restriction from EMBASE databases, PubMed and the Cochrane Library from their inception to April, 2016. Search terms included “pancreaticoduodenectomy”, “pancreatoduodenectomy”, “pancreatic resection”, “pancreatic anastomosis”, “pancreaticogastrostomy”, “Whipple”, “PD”, “pancreatic fistula” combined with “stent” or “stents” or “stenting”. We also reviewed the reference lists of the included studies for undetected relevant studies.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) original research from RCT among adults; (2) the intervention of interest was internal, external or no transanastomotic pancreatic ductal stenting for PD; (3) the participants of interest was patients with pancreaticoduodenectomy; (4) the primary outcome of interest was pancreatic fistula and the second outcome was other postoperative complications; (5) Odds Ratio (OR) with 95% confidence interval (CI) of the risk of postoperative complications was provided or could be calculated; (6) the most recent and complete study was included if data from the same population had been published more than once. And the exclusion criteria: (1) participants were animals, children or pregnancy, (2) absence of the data of the primary and secondary outcomes, (3) the publication type was case reports, conference abstracts or review, (4) participants with an operative history in 3 years.

Two investigators searched and reviewed all identified studies independently. If the two investigators cannot reach a consensus about the eligibility of an article, it was resolved by disputing with a third reviewer.

Data extraction and quality assessment

The following data were extracted from each study by two investigators independently: the first author’s name, publication year, country where the study was performed, study design, the type of surgery, age range or mean age, number of participants and deaths, postoperative complications, anastomosis technique. The Jadad scoring system, an instrument for assessing the quality of RCT, was used for assessing each included trial according to the descriptions of randomization, blinding, and withdrawals in the trials. Each study can be awarded a score from one point to seven points.

Statistical analysis

The direct meta-analysis was conducted by RevMan software version 5.3 (The Nordic Cochrane Centre, Cochrane Collaboration, and Copenhagen, Denmark). Odds Ratio with 95% confidence interval was calculated to compare the incidence of postoperative complications and death between the external, internal or no stenting group. Heterogeneity among the included studies was qualitatively evaluated using x2-based Q test. P value less than 0.05 showed that there was statistically significant heterogeneity across the studies. The level of heterogeneity between studies was evaluated by I² statistics. I²<30% was considered to be low heterogeneity, otherwise was considered to be moderate or high heterogeneity. Taking a conservative approach, we used a random effects model for all pair-wise meta-analysis. We performed the Bayesian network meta-analysis with JAGS software in R and GeMTC package of R (version 3.3.2) by the method of Markov chain Monte Carlo. Convergence of a consistency model was achieved with the first
5,000 iterations as burn-in phase and 50,000 simulation iterations. A node-splitting analysis, contrasting direct and indirect evidence of comparison from each result, was implemented to assess inconsistency of the network analysis. Ranking probabilities of presence of postoperative complications and death for each treatment, was estimated by the hierarchy summarized as surface under the cumulative ranking curve.

Result

Search results and study characteristics

A total of 1530 articles were retrieved by searching electronic databases and manual searching relevant reference lists. After duplicates were differentiated and excluded, 937 articles were left. We excluded unrelated review, case report, systematic review and meta-analysis, and obviously not relevant studies according to the title or abstract, 245 articles were left. Hence, 8 articles were used in this meta-analysis after full text screening [8, 14, 16, 18-22]. The detailed steps of our literature search were shown in Figure 1. Eight studies with a total of 1295 patients were included in the final analysis. The sample size of all included studies ranged from 43 to 328. In total, 602 patients received external stenting, 344 patients received internal stenting and 302 patients received no stenting. 3 studies came from Japan, 2 from China, 3 from Korea, France and America. The characteristics of these studies are presented in Table 1.

Direct meta-analysis

As showed in the Figure 2, there was no significant difference between external stenting group and internal stenting group in terms of postoperative pancreatic fistula rate (OR=0.81, 95% CI=0.47, 1.39, p=0.44). And heterogeneity was a little high (I²=51%, p=0.10). The same result was emerged in the comparison for postoperative delayed gastric emptying rate (OR=0.74, 95% CI=0.30, 1.83, p=0.51) with a higher heterogeneity (I²=61%, p=0.05). Similarly in terms of morbidity (OR=1.05, 95% CI=0.46, 2.41, p=0.91) and mortality (OR=0.77, 95% CI=0.20, 2.91, p=0.70), the external stenting did not show significant advantages over than internal stenting whereas there was a less number of involved studies (only 3 for morbidity and 2 for mortality).

Figure 3 showed the comparison of external stenting and no stenting after pooling of data from three RCTs. External stenting group had a lower incidence of postoperative pancreatic fistula than without stenting group (OR=0.42, 95% CI=0.25, 0.70, p=0.0008) and there was no heterogeneity (I²=0%, p=0.75). Nevertheless, in terms of postoperative delayed gastric...
Table 1. Characteristics of studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>Surgery</th>
<th>Stenting type</th>
<th>Patients (n)</th>
<th>Age (years) (median and 95 per cent CI or SD)</th>
<th>PF, pancreatic fistula (A/B/C)*</th>
<th>Quality Score (Jadad system)</th>
</tr>
</thead>
<tbody>
<tr>
<td>J Jang et al</td>
<td>2016</td>
<td>Korea</td>
<td>RCT</td>
<td>PD/PPPD</td>
<td>EXS</td>
<td>164</td>
<td>62.0 (46.3, 76.0)</td>
<td>35/39/1</td>
<td>3</td>
</tr>
<tr>
<td>Tani et al</td>
<td>2010</td>
<td>Japan</td>
<td>RCT</td>
<td>PD</td>
<td>EXS</td>
<td>50</td>
<td>70 (44-87)</td>
<td>7/2/1</td>
<td>4</td>
</tr>
<tr>
<td>Kamoda et al</td>
<td>2008</td>
<td>Japan</td>
<td>RCT</td>
<td>PD/PPPD</td>
<td>EXS</td>
<td>22</td>
<td>9/13 (≥65/&lt;65)</td>
<td>6/2/0</td>
<td>4</td>
</tr>
<tr>
<td>Wang et al</td>
<td>2014</td>
<td>China</td>
<td>RCT</td>
<td>PD/PPPD</td>
<td>EXS</td>
<td>110</td>
<td>52/58 (≥65/&lt;65)</td>
<td>10/4/1</td>
<td>3</td>
</tr>
<tr>
<td>Patrick et al</td>
<td>2011</td>
<td>France</td>
<td>RCT</td>
<td>PD</td>
<td>EXS</td>
<td>77</td>
<td>60.8 ± 11.8</td>
<td>1/13/6</td>
<td>4</td>
</tr>
<tr>
<td>Ronnie et al</td>
<td>2007</td>
<td>Hong Kong</td>
<td>RCT</td>
<td>PD</td>
<td>EXS</td>
<td>60</td>
<td>61 ± 12</td>
<td>4 (NA)</td>
<td>3</td>
</tr>
<tr>
<td>Motoi et al</td>
<td>2012</td>
<td>Japan</td>
<td>RCT</td>
<td>PPPD/PD</td>
<td>EXS</td>
<td>119</td>
<td>66.0 (33-79)</td>
<td>7 (NA)</td>
<td>3</td>
</tr>
<tr>
<td>Jordan et al</td>
<td>2006</td>
<td>America</td>
<td>RCT</td>
<td>PPPD/PD</td>
<td>INS</td>
<td>47</td>
<td>63 (27-89)</td>
<td>13 (NA)</td>
<td>3</td>
</tr>
</tbody>
</table>

*values are International Study Group on Pancreatic Fistula (ISGPF) classification of pancreatic fistula; PF, pancreatic fistula; RCT, randomized clinical trial; PD, pancreaticoduodenectomy; EXS, external stent; INS, internal stent; NS, no stent; PJ, pancreaticojejunostomy; PPPD, pylorus-preserving pancreaticoduodenectomy.
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Figure 2. Direct meta-analysis of external stenting versus internal stenting for the result of (A) Pancreatic Fistula, (B) Delayed Gastric Emptying, (C) Morbidity, (D) Mortality.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>external stenting</th>
<th>no stenting</th>
<th>Odds Ratio</th>
<th>M-H. Random, 95% CI</th>
<th>M-H. Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moto 2012</td>
<td>7</td>
<td>47</td>
<td>16</td>
<td>46</td>
<td>24.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.46 [0.14, 1.11]</td>
<td></td>
</tr>
<tr>
<td>Patrick 2011</td>
<td>20</td>
<td>77</td>
<td>34</td>
<td>61</td>
<td>57.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.46 [0.25, 0.85]</td>
<td></td>
</tr>
<tr>
<td>Ronnie 2007</td>
<td>4</td>
<td>60</td>
<td>12</td>
<td>60</td>
<td>18.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.26 [0.09, 0.64]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>184</td>
<td>187</td>
<td>100.0%</td>
<td>0.42 [0.25, 0.70]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>31</td>
<td>60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\tau^2=0.00$, $\chi^2=0.58$, df=2 ($p=0.79$), $I^2=0$%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z=3.34$ ($p=0.0008$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 3. Direct meta-analysis of external stenting versus no stenting for the result of (A) Pancreatic Fistula, (B) Delayed Gastric Emptying, (C) Morbidity, (D) Mortality.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>external stenting</th>
<th>no stenting</th>
<th>Odds Ratio</th>
<th>M-H. Random, 95% CI</th>
<th>M-H. Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moto 2012</td>
<td>6</td>
<td>47</td>
<td>5</td>
<td>46</td>
<td>32.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.20 [0.34, 4.24]</td>
<td></td>
</tr>
<tr>
<td>Patrick 2011</td>
<td>6</td>
<td>77</td>
<td>22</td>
<td>81</td>
<td>37.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.23 [0.05, 0.60]</td>
<td></td>
</tr>
<tr>
<td>Ronnie 2007</td>
<td>5</td>
<td>60</td>
<td>3</td>
<td>60</td>
<td>29.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.75 [0.33, 7.56]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>184</td>
<td>187</td>
<td>100.0%</td>
<td>0.71 [0.19, 2.69]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>17</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\tau^2=0.57$, $\chi^2=7.01$, df=2 ($p=0.003$), $I^2=71$%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z=0.50$ ($p=0.62$)</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Emptying rate (OR=0.71, 95% CI=0.19, 2.69, p=0.62), morbidity (OR=0.64, 95% CI=0.41, 1.01, p=0.05) and mortality (OR=0.87, 95% CI=0.26, 2.98, p=0.83), we found out no significant difference between external and no stenting group.

Network meta-analysis and rank probability analysis

Figure 4 showed the results of network meta-analysis, and no inconsistency between direct and indirect estimates in all comparisons (p<0.05 for all results). In terms of postoperative pancreatic fistula, no matter internal stenting (OR=1.4, 95% CrI=0.78, 2.7) or no stenting (OR=1.7, 95% CrI=0.85, 3.7) showed a higher incidence of that than external stenting, whereas the difference were not significant. The result of network meta-analysis for the comparison of external and no stenting was a little different from the result of direct meta-analysis (Figure 4A). And internal stenting also did not showed lower incidence of pancreatic fistula than no stenting (no stenting vs internal stenting, OR=1.2, 95% CrI=0.52, 2.9). In cases of delayed gastric emptying rate, we found external, internal and no stenting group had a similar effect on the decrease of that. Compared with no stenting, internal stenting showed almost
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As showed in the Figure 5, external stenting group had the lowest probabilities of being ranked first in almost all comparisons (1.6% for pancreatic fistula, 8.6% for DGE, 8.4% for morbidity and 23.5% for mortality). And no stenting group had the highest probabilities of being ranked first in all comparisons (69.1% for pancreatic fistula, 48.9% for DGE, 77.8% for morbidity and 55.4% for mortality). In this analysis, external stenting was evaluated to be the most safe strategy but without significant difference with others.

Discussion

Placement of transanastomotic pancreatic ductal stents was first described in 1980s. Surgeons inserted a tube made from vinyl chloride into the main duct of pancreas to drainage pancreatic juice outside when performing pancreaticojejunal anastomosis during PD [23]. To date, this technique has been widespread in many high-volume centers and utilized as an optimum surgical intervention to prevent PF following PD [12, 14]. The pancreaticojejunal anastomosis will have essential time to heal with the transanastomotic pancreatic ductal stents preventing pancreatic enzymes from being activated by pancreatic juice. Whereas the evidences to support advantages of stenting over than no stenting were still limited. Recently, Dong et al performed a direct meta-analysis to compare the effectiveness of decreasing PF rate for stenting and no stenting [24]. No matter external stenting or internal stenting got a significant decreased PF rate than no stenting. This result was contradictory to several previous studies which concluded benefits of stenting on decreasing PF [16]. Therefore we performed a network meta-analy-
sis to compare all three strategies (external stenting, internal stenting and no stenting) together with only RCTs.

External pancreatic ductal stenting has been evaluated to be one effective type of trans-anastomotic stenting in several studies. In comparison to internal and no stenting, the first advantage of that is the completely drainage of pancreatic juice to outside thus avoiding the corrosive effect arose from pancreatic enzymes activated by the mixture of bile, pancreatic juice and intestinal juice [25]. Whereas the loss of digestive enzyme and massive pancreatic juice may lead to dysfunction of endocrine and dilatation of pancreatic duct, even delay of the recovery of gastrointestinal function, which are not exist in internal stenting patients whose pancreatic juice was reserved by stenting [26]. The second advantage, by alleviating high tension and improving the supply of blood of the tissue in anastomosis site, external stenting can prevent necrosis and ischemia [19]. The third one is very convenient to check the volume, color and characteristics of the drainage fluid of pancreatic juice [27]. Another superiority of placing stents externally is the decrease of proximal migration rate which could be a risk of pancreatitis and pancreatolithiasis.

Figure 5. Ranking probability analysis for the result of (A) Pancreatic Fistula, (B) Delayed Gastric Emptying, (C) Morbidity, (D) Mortality; A was external stenting, B was internal stenting and C was no stenting. There were three columns in each treatment group of this figure. Take the columns of treatment A in (A) as an example, the first column represented the probability to be rank first in the incidence of pancreatic fistula, the meanings of the second and third columns were similar.
A number of clinicians recommended the use of external stenting as a standard transanastomotic pancreatic ductal stenting. Nevertheless, disadvantages of external stenting are also non-negligible. The occurrence of pancreatitis or late-onset stenosis resulted from removal of external stents could be the first disadvantage. Meanwhile drain-related infections or bowel injury will be the second disadvantage. And the hole that connected the anastomosis site with in vitro for placement of external stents may be associated with leakage of bowel contents after stents removal. Our study showed external stenting had a significant lower PF rate than no stenting but not internal stenting in the direct meta-analysis. In the network-meta analysis, external stenting group had the lowest probabilities of being ranked first in PF, whereas the benefit of external stenting was not significant.

Whether to prevent PF effectively should be one of the most important ‘touchstones’ for the application of transanastomotic pancreatic ductal stenting. Which method among external stenting, internal stenting and no stenting is preferable is still inconsistent. Some retrospective studies and RCT revealed external stenting could decrease the rate of PF significantly when compared with internal stenting [19, 28] while some demonstrated internal stenting was associated with a lower incidence of PF [18, 27]. Previous meta-analysis assessed this problem with some methodological limits. Zhou et al reported a trend toward lower rate of PF in external stenting group based on the indirect system comparison between results of external versus no stenting and internal versus no stenting. Moreover there are only three studies with low quality (only one randomized controlled trial) in terms of internal versus no stenting which may lead to underlying selected bias and unreliable results. Ke et al revealed external stenting had a benefit on decreasing PF rate compared with internal stenting by pooling of data from RCTs and retrospective studies overall [16]. The randomized controlled trials and retrospective studies have different methods of design and assessment of quality therefore a potential bias may occur in result of the foregoing study. Meanwhile the small number of participants in randomized controlled trials which are deemed high level of evidence could be another major limitation.

In our network meta-analysis, there was no significant difference between external, internal and no stenting group in terms of pancreatic fistula and other results. Nevertheless, the ranking probability analysis showed external stenting had the highest probabilities to be the safest one among the three methods. And even internal stenting had a better rank than no stenting, meanwhile, this result might be influenced by that the number of studies of comparing internal stenting and no stenting were less. This may prompt us that pancreatic ductal stenting still have some value which were limited by the lack of researches on that.

There were several limitations in this meta-analysis, which should be taken into consideration when interpreting our results. Firstly, the heterogeneity of several results was bit high; secondly, the number of involved studies was insufficient for several analysis such as the analysis of morbidity and mortality. Thirdly, the participants were mostly from Asia region because of limited information. Fourthly, different anastomotic technique was applied in involved studies. The last but not the least was publication bias which may influence the authenticity of our results.

**Conclusions**

There was no significant difference between external, internal and no stenting group following pancreaticoduodenectomy in terms of postoperative pancreatic fistula, delayed gastric emptying rate, morbidity and mortality in the pooling analysis of both RCTs and OCS. The current meta-analysis suggests that internal and no stenting appears to be the same effective as external stenting for patients undergoing PD in terms of postoperative pancreatic fistula, delayed gastric emptying rate, morbidity and mortality. We still need further multi-center randomized controlled trials to prove that.

**Disclosure of conflict of interest**

None.

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