Measures to Prevent Pancreatic Fistula After Pancreatoduodenectomy

A Comprehensive Review

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Objective: To review the current evidence on the efficacy of various interventions directed toward prevention of pancreatic fistula after pancreatoduodenectomy.

Data Sources: A MEDLINE database search from January 1, 1990, to August 31, 2008, was performed to identify relevant articles using the keywords pancreatoduodenectomy, pancreaticojejunostomy, pancreaticogastrostomy, pancreatic anastomotic leakage, and pancreatic fistula. Additional articles were identified by a manual search of the references from the key articles.

Study Selection: Case reports were excluded from this study.

Data Extraction: Of the identified studies, only those published in English describing meta-analyses or randomized controlled trials were considered first. In those aspects with limited or no randomized controlled trials, nonrandomized comparative studies and case series were included also.

Data Synthesis: The prophylactic use of perioperative somatostatin and its analogues to prevent pancreas-related complications after pancreatic surgery remains controversial and does not result in a reduction of operative mortality. There is no clear evidence for or against a particular type of pancreaticoenteric anastomosis. Pancreaticogastrostomy cannot be replaced by pancreatic ductal obliteration. Pancreaticogastrostomy is equivalent to pancreaticojejunostomy in perioperative morbidity and mortality.

Conclusion: More large-scale comparative studies and randomized controlled trials are required to determine the optimum pharmacologic interventions and technique of pancreaticoenteric anastomosis after pancreatoduodenectomy.

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In 1898, Halsted performed the first local excision of carcinoma of ampulla of Vater. In 1909, the first successful regional resection of a periampullary tumor was performed by Kausch. He performed the operation as a 2-stage procedure in which a cholecystojejunostomy was performed 6 weeks before the second operation, which involved resection of the head of the pancreas, the pylorus, and the first and second parts of the duodenum, followed by gastroenterostomy, closure of the distal common bile duct, and anastomosis of the residual pancreas to the third part of the duodenum. Resection of periampullary tumor was popularized in a 1935 article by Whipple and colleagues. Their 2-stage pancreateoduodenectomy consisted of posterior gastroenterostomy, ligation and division of the common bile duct and cholecystogastrostomy in the first stage, followed by resection of the duodenum and pancreatic head in the second stage. The pancreatic stump was closed with sutures, without a pancreaticoenteric anastomosis. Whipple later completed the whole procedure in a single stage in 1940, and the reconstruction was modified in 1942 to include pancreaticojejunostomy, as he found a high rate of pancreatic fistula after closure of pancreatic stumps. Improvements in anesthesia and perioperative management decreased the surgical mortality to less than 5% for pancreateoduodenectomy. Unfortunately, the postoperative morbidity remains high and approaches 50% even in large series. The key determinant of outcome after pancreateoduodenectomy remains the pancreaticoenteric anastomosis. Sepsis and hemorrhage, caused by pancreatic fistula, are associated with mortality of 20% to 40% and result in prolonged hospitalization and increased hospital expenses. The terminology in the medical literature to de-
scribe pancreatic fistula, pancreatic leakage, or anastomotic insufficiency is confusing, and the terms have been interchangeably used. The reported pancreatic fistula rate ranged from 2% to 22% depending on the definition used. However, there is no universally accepted definition of pancreatic fistula. A uniform definition is urgently needed to make results comparable between different series. An international panel of pancreatic surgeons from well-known centers (the International Study Group on Pancreatic Fistula Definition12) worked together to develop a simple, objective, and easy-to-apply definition of postoperative pancreatic fistula, graded primarily on clinical effect. An all-inclusive definition is a drain output of any measurable volume of fluid on or after postoperative day 3 with an amylase content greater than 3 times the serum amylase activity.

Several pharmacologic and technical interventions have been suggested to decrease the pancreatic fistula rate, but the results have been controversial. The only consistently reproducible factor is the establishment of specialist centers performing pancreatic surgery in high volume.13-18 This article reviews the current evidence on the efficacy of various interventions directed toward prevention of pancreatic fistula after pancreatoduodenectomy.

SEARCH STRATEGY

A MEDLINE database search from January 1, 1990, to August 31, 2008, was performed to identify relevant articles using the keywords pancreatoduodenectomy, pancreaticojejunostomy, pancreatico-gastrostomy, pancreatic anastomotic leakage, and pancreatic fistula. Additional articles were identified by a manual search of the references from the key articles.

Of the identified studies, only those published in English describing meta-analyses or randomized controlled trials (RCTs) were considered first. In those aspects with limited or no RCTs, nonrandomized comparative studies and case series were included also. Only full peer-reviewed articles were selected. Two of us (E.C.H.L. and W.Y.L.) independently identified and screened the search findings for potentially eligible articles. Any disagreement was discussed and a consensus reached.

INCLUSION AND EXCLUSION CRITERIA

Only studies about pancreatoduodenectomy reporting the outcomes of pancreatic fistula rates or pancreatic-related complications were selected. Case reports were excluded.

DATA ANALYSIS

Level of evidence was graded according to the following hierarchy of evidence developed by the National Health and Medical Research Council of Australia19 (hereafter evidence levels 1-4): (1) Evidence obtained from a systematic review of all relevant RCTs. (2) Evidence obtained from at least 1 properly designed RCT. (3) (a) Evidence obtained from well-designed pseudo-RCTs (alternate allocation or some other method). (b) Evidence obtained from cohort studies, case-control studies, interrupted time series with a control group, or comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomized. (c) Evidence obtained from comparative studies with historical control, 2 or more single-arm studies, or interrupted time series without a parallel control group. (4) Evidence obtained from case series (either posttest or pretest and posttest).

RISK FACTORS

In an attempt to prevent pancreatic fistula after pancreatoduodenectomy, some risk factors have been identified. These include pancreas risk factors (pancreatic texture, pancreatic duct size, blood supply to the stump, volume of pancreatic juice output, and pathologic features), patient risk factors (age, sex, bilirubin level, and comorbid illness), and operation risk factors (operating time, blood loss, type of anastomosis, and stent use).20-35 Among these risk factors, pancreatic texture, pancreatic duct size, blood supply to the stump, and volume of pancreatic juice output have been considered the most significant. It is generally accepted that a fibrotic pancreatic remnant facilitates the pancreaticoenteric anastomosis, whereas a soft pancreatic remnant frequently results in a higher pancreatic fistula rate.

PHARMACOLOGIC INTERVENTION

Somatostatin is a potent inhibitor of pancreatic endocrine and exocrine functions. The synthetic peptide octreotide contains the same amino acid sequences essential to the activity of somatostatin, while conferring resistance to enzyme degradation, resulting in a long-acting stable analog suitable for subcutaneous administration. The rationale is that, by decreasing the volume of pancreatic secretion, the pancreatic fistula rate would be decreased because the pancreaticoenteric anastomosis would heal better. Adverse effects of somatostatin and its analogues include nausea, flatulence, diarrhea, steatorrhea, pain at the injection site, and abdominal discomfort.

There were 11 RCTs involving 2023 patients who examined the use of somatostatin and its analogues (Table 1).34-44 Five RCTs from Europe34-36,39 and 1 RCT from Asia42 showed the benefit of perioperative use of somatostatin and its analogues to decrease the postoperative complication rate. On the other hand, 2 recent RCTs from Europe37,44 and 3 RCTs from the United States38,39,41 failed to show a benefit. Two recent meta-analyses45,46 have been published. Connor et al45 analyzed 10 studies and showed that somatostatin and its analogues did not reduce mortality after pancreatic surgery but reduced total morbidity and pancreas-specific complications. Somatostatin and its analogues reduced the rate of biochemical fistula but not the incidence of clinical anastomotic disruption. Alghamdi et al46 analyzed 7 studies and showed that perioperative octreotide administration was associated with a significant reduction of the pancreatic fistula rate after pancreatic surgery. However, this risk reduction was not associated with a significant difference in postoperative morality. Conclusions drawn from these meta-analyses should be cautious, as pooling of data from these RCTs was difficult because there was considerable heterogeneity in these studies for end point measures, definition of outcome measurements, treatment...
regimens, pathologic findings, types of pancreatic surgery, and anastomotic technique.

Prophylactic use of perioperative somatostatin and its analogues to prevent pancreas-related complications after pancreatic surgery remains controversial. It does not result in a reduction of operative mortality. There is a need for RCTs with standardization in definition of outcome measurements, treatment regimen, surgical technique, and stratification of risk factors (evidence levels 1 and 2).

**Table 1. Randomized Controlled Trials Comparing Outcomes of the Use of Somatostatin and Its Analogues in Pancreatic Resection**

<table>
<thead>
<tr>
<th>Source</th>
<th>Type of Study</th>
<th>Treatment Group vs Control Group, No.</th>
<th>Pancreatoduodenectomy</th>
<th>Pancreatic Fistula</th>
<th>Overall Complications</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Büchler et al, 1992 (Germany)</td>
<td>Multicenter trial</td>
<td>125 vs 121</td>
<td>81.3</td>
<td>16.6 vs 28</td>
<td>22 vs 55.4</td>
<td>3.2 vs 5.8</td>
</tr>
<tr>
<td>Pederzoli et al, 1994 (Italy)</td>
<td>Multicenter trial</td>
<td>122 vs 130</td>
<td>69.5</td>
<td>9 vs 18.5</td>
<td>15.6 vs 29.2</td>
<td>1.6 vs 3.8</td>
</tr>
<tr>
<td>Montorsi et al, 1995 (Italy)</td>
<td>Multicenter trial</td>
<td>111 vs 107</td>
<td>65.6</td>
<td>9 vs 19.6</td>
<td>21.6 vs 36.4</td>
<td>8.1 vs 5.6</td>
</tr>
<tr>
<td>Friess et al, 1994 (Switzerland)</td>
<td>Multicenter trial</td>
<td>122 vs 125</td>
<td>50.2</td>
<td>12 vs 28</td>
<td>16.4 vs 29.6</td>
<td>1.6 vs 0.8</td>
</tr>
<tr>
<td>Lowy et al, 1997 (United States)</td>
<td>Single-center trial</td>
<td>57 vs 53</td>
<td>100.0</td>
<td>12 vs 6</td>
<td>30 vs 25</td>
<td>2 vs 0</td>
</tr>
<tr>
<td>Yeo et al, 2000 (United States)</td>
<td>Single-center trial</td>
<td>104 vs 107</td>
<td>100.0</td>
<td>11 vs 9</td>
<td>40 vs 34</td>
<td>1 vs 0</td>
</tr>
<tr>
<td>Guillett et al, 2001 (France)</td>
<td>Multicenter trial</td>
<td>38 vs 37</td>
<td>100.0</td>
<td>5.3 vs 21.6</td>
<td>21.1 vs 35.1</td>
<td>5.3 vs 2.7</td>
</tr>
<tr>
<td>Sarr et al, 2003 (United States)</td>
<td>Multicenter trial</td>
<td>135 vs 140</td>
<td>78.2</td>
<td>24 vs 23</td>
<td>40 vs 42</td>
<td>0 vs 1.4</td>
</tr>
<tr>
<td>Shan et al, 2003 (Asia)</td>
<td>Single-center trial</td>
<td>27 vs 27</td>
<td>100.0</td>
<td>7.4 vs 7.4</td>
<td>26 vs 52</td>
<td>3.7 vs 3.7</td>
</tr>
<tr>
<td>Suc et al, 2004 (France)</td>
<td>Multicenter trial</td>
<td>122 vs 108</td>
<td>77.0</td>
<td>17 vs 19</td>
<td>29 vs 37</td>
<td>12 vs 7</td>
</tr>
<tr>
<td>Hesse et al, 2005 (Belgium)</td>
<td>Single-center trial</td>
<td>55 vs 50</td>
<td>76.2</td>
<td>9.1 vs 8</td>
<td>10.9 vs 12</td>
<td>1.8 vs 0</td>
</tr>
</tbody>
</table>

a Pancreas related, 15.3% vs 29.9%.
b Pancreas related, 13.2% vs 32.4%.
c Pancreas related, 30.4% vs 26.4%.
d Pancreas related, 22% vs 48%.
e Intra-abdominal complications, 22% vs 32%.

In an attempt to obviate a pancreaticoenteric anastomosis, pancreatic duc tally occlusion was studied. There were 2 RCTs, 47,48 In the study by Reissman et al,47 the pancreaticojejunostomy group with 18 patients underwent end-to-end anastomosis of pancreaticojejuno stomy, while the ductal occlusion group with 17 patients underwent primary closure of the pancreatic duct, oversewing of the pancreatic stump, and external drainage. The ductal occlusion group had lower morbidity (56% vs 24%), decreased mortality (11% vs 0%), and a shorter hospital stay (42.2 vs 26.4 days). However, the study population was small. In the study by Tran et al,48 a total of 83 patients received pancreaticojejunostomy, while 86 patients received chemical and suture occlusion of the pancreatic duct. No significant difference was found in postoperative complications, mortality, or exocrine insufficiency. The pancreatic fistula rate was significantly higher in the ductal occlusion group (5% vs 17%). After 3 and 12 months, there were significantly more patients with diabetes mellitus in the ductal occlusion group. So far, insufficient evidence exists to show that pancreaticoenteric anastomosis can be replaced by pancreatic ductal obliteration (evidence level 2).

**PANCREATICOGASTROSTOMY**

Waugh and Clagett49 first used pancreaticogastrostomy in clinical practice in 1946. Pancreaticogastrostomy has gained favor in recent years as a possible means of reducing the incidence of pancreatic fistula.28,50-55 Proponents have noted several potential advantages. Pancreatic enzymes are inactivated by the gastric acidic environment, and the stomach does not contain enterokinase, which is required for conversion of trypsinogen to trypsin and subsequent activation of other proteolytic enzymes. A lack of enzyme activation may help prevent autodigestion of the anastomosis. Furthermore, the proximity of the pancreas to the posterior stomach wall allows for potentially less tension on the anastomosis. The excellent blood supply to the stomach wall is favorable to anastomotic healing, and the thickness of the stomach wall holds sutures well.

There have been 3 RCTs comparing pancreaticogastrostomy with pancreaticojejunostomy (Table 2).28,34,55 They failed to show any significant difference regarding pancreatic fistula rates, postoperative complications, or mortality. Two recent meta-analyses56,57 attempted to solve this controversy. The study by McKay et al56 analyzed 11 articles, including 1 RCT, 2 prospective nonrandomized trials, and 8 cohort studies. The study findings suggested that pancreaticogastrostomy was safer than pancreatectoduodenectomy, but much of the evidence came from cohort studies. The study by Wente et al57 analyzed 16 articles, including 3 RCTs. The results indicated that all cohort studies reported superiority of pancreaticogastrostomy over pancreaticojejunostomy, most likely influenced by publication bias. In contrast, all RCTs failed...
to show an advantage of a particular technique, suggesting that both techniques were equally good. Based on the current evidence, pancreaticogastrostomy and pancreaticojejunostomy are equivalent in terms of perioperative outcome (evidence levels 1 and 2).

**PANCREATICOJEJUNOSTOMY**

Pancreateicojejunostomy has been the most commonly used method of pancreaticoenteric anastomosis after pancreatectoduodenectomy. Apart from the different positions of the jejunal loop (antecolic, retrocolic, or retro-mesenteric) and the other variations, such as the isolated Roux loop pancreateicojejunostomy, the anastomosis can be performed as an end-to-end anastomosis with invagination of the pancreatic stump in the jejunum or as an end-to-side anastomosis with or without duct-to-mucosa suturing. There are more variations of these 2 anastomotic techniques. An internal or external pancreatic duct stent may or may not be placed across these anastomoses. There is no firm evidence to show which technique is superior.

**ISOLATED ROUX LOOP PANCREATEICOJEJUNOSTOMY**

Separation of the pancreateicojejunal and hepaticojejunal anastomoses by an isolated Roux loop reconstruction was advocated to minimize the incidence and severity of anastomotic erosion by pancreatic juice activated by bile. Potential disadvantages are increased operating time and the need for an additional anastomosis. Several cohort studies have reported a low pancreatic fistula rate and its related mortality. In the only nonrandomized study, by Kaman et al., the data failed to show any significant difference in the pancreatic fistula rates (10% vs 12%) following the isolated Roux loop pancreateicojejunal reconstruction or conventional single-loop pancreateicojejunal reconstruction after pancreatectoduodenectomy. Based on the limited evidence, the use of isolated Roux loop pancreateicojejunostomy cannot prevent pancreatic fistula formation (evidence levels 3b and 4).

**PANCREATIC DUCT STENTING**

One of the technical modifications in pancreaticoenteric anastomosis is the use of a transanastomotic stent for internal or external drainage of pancreatic secretion. The potential advantages of a pancreatic stent include diversion of pancreatic secretion from the anastomosis and facilitation for more precise placement of sutures during the anastomosis, thus protecting the pancreatic duct from suture injury and reducing the risk of iatrogenic pancreatic duct occlusion. However, complications such as obstruction of the stent leading to pancreatic fistula and migration of the stent are drawbacks with transanastomotic stenting. The number of studies on pancreatic stenting is limited, and the results are conflicting.

Internal transanastomotic stenting was reported to reduce the pancreatic fistula of pancreateicojejunal anastomosis in the cohort study by Yoshimi et al. However, in the nonrandomized study by Imaizumi et al. with 168 patients, there was no significant difference in the pancreatic fistula rates between the end-to-side pancreateicojejunostomy of normal soft pancreas using the stented (internal or external) methods vs the nonstented methods (5.7% vs 6.7%). The internal pancreatic stent was evaluated by Winter et al. in an RCT among 234 patients. The study showed that internal pancreatic duct stenting did not decrease the frequency or the severity of postoperative pancreatic fistulas. The pancreatic fistula rates in patients undergoing pancreatectoduodenectomy with and without an internal pancreatic stent were 11.3% and 7.6%, respectively.

An external stent has the theoretical advantage of more complete diversion of pancreatic secretion away from the pancreateicojejunal anastomosis and prevents the activation of pancreatic enzymes by bile. The nonrandomized study by Ohwada et al. showed equivalent outcomes for external and internal pancreatic stenting of duct-to-mucosa pancreateicojejunal anastomosis after pancreatectoduodenectomy. The RCT by Poon et al. among 120 patients showed that the externally stented group had a significantly lower pancreatic fistula rate compared with the nonstented group (6.7% vs 20%).

Based on the current evidence, it is unclear whether drainage of the pancreatic duct with a stent can reduce the pancreatic fistula rate after pancreatectoduodenectomy (evidence levels 2 and 3b).

**COMPARISON OF DIFFERENT ANASTOMOTIC TECHNIQUES**

Few nonrandomized studies and RCTs have compared the various surgical techniques. Most are cohort studies. To date, no RCT has demonstrated that duct-to-mucosa anastomosis was superior to invagination anastomosis. The RCT by Bassi et al. found no significant differences in abdominal complication rates (35% vs 38%) or pancreatic fistula rates (13% vs 15%) between 72 patients randomized to duct-to-mucosa anastomosis vs 72 patients randomized to end-to-side single-layer pancreateicojejunal anastomosis technique. The invagination technique for the more difficult soft pancreatic stump and

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**Table 2. Randomized Controlled Trials Comparing Pancreaticogastrostomy vs Pancreaticojejunostomy**

<table>
<thead>
<tr>
<th>Source</th>
<th>Type of Study</th>
<th>Pancreaticogastrostomy vs Pancreaticojejunostomy, N.</th>
<th>Pancreatic Fistula</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yeo et al.28 1995</td>
<td>Single-center trial</td>
<td>73 vs 72</td>
<td>12 vs 11</td>
<td>49 vs 43</td>
<td>0 vs 0</td>
</tr>
<tr>
<td>Duffas et al.54 2005</td>
<td>Multicenter trial</td>
<td>81 vs 68</td>
<td>16 vs 20</td>
<td>46 vs 47</td>
<td>12 vs 10</td>
</tr>
<tr>
<td>Bassi et al.55 2005</td>
<td>Single-center trial</td>
<td>69 vs 82</td>
<td>13 vs 16</td>
<td>29 vs 39</td>
<td>0 vs 1</td>
</tr>
</tbody>
</table>

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small pancreatic duct has been advocated by most authors, preserving the duct-to-mucosa anastomosis for the firm pancreatic stump and large pancreatic duct.

Peng et al\textsuperscript{72,80} proposed that pancreatic fistula starts at a point where a needle inadvertently penetrates a pancreatic ductule or a suture lacerates the fragile pancreatic parenchyma on suturing or tying a knot. The resultant minor leak in pancreatic juice gradually leads to gross leakage as a consequence of autodigestion around the anastomosis. Based on this hypothesis, Peng et al\textsuperscript{80} described a binding pancreaticojejunal anastomosis technique with a pancreatic fistula rate of 0%. In brief, the stump of the jejunum was everted for a length of 3 cm. The jejunal mucosa was destroyed by applying 10% carboxylic acid (subsequently rinsed with 75% alcohol and isotonic sodium chloride solution) or by diathermy coagulation. The remnant of the pancreas was dissected for a distance of greater than 3 cm from its cut edge. The cut edge of the pancreatic stump and the everted jejunum were anastomosed with 3-0 silk in a circular fashion, and care was taken to suture the jejunal mucosa only to avoid penetrating into the muscular and serosal layers. The posterior lip of the pancreatic duct should be involved in the posterior row of suture whenever technically possible. The everted jejunum was restored to its normal position to wrap over the pancreatic stump. An absorbable ligature was then passed around the jejunum, with the invaginated pancreatic stump, ensuring an adequate blood supply to the pancreatic stump as described by Strasberg and McNevin\textsuperscript{21} and by Strasberg et al.\textsuperscript{22} The pancreatic neck contains a vascular watershed. The head is supplied by the gastroduodenal and superior mesenteric arteries, which form the pancreaticoduodenal arcades. The body is supplied by branches of the splenic artery. Branches from these 2 zones of arterial supply meet in the neck of the pancreas. There are common anomalies in which the arterial supply to the neck and the adjacent part of the body comes from vessels other than the splenic artery. These vessels may be interrupted during pancreaticoduodenectomy, and consequent relative ischemia may develop at the pancreaticojejunal anastomosis if the anastomosis is made at the end of the pancreatic stump. Because there is a vascular watershed at the neck of the pancreas, moving the plane of transection toward the left improves the blood supply to the pancreatic cut end. Our anastomosis between the jejunal cut end and the pancreatic stump is made 4 cm from the cut end of the pancreatic stump, ensuring an adequate blood supply to the anastomosis. We have been using this technique, which can be performed reliably with few complications, in clinical practice. In the cohort study by Chen et al\textsuperscript{79} with 52 consecutive patients, the pancreatic fistula rate after this modified invagination technique of anastomosis was 0%. The favorable results of this technique warrant further investigation in large prospective studies and RCTs. Based on the current evidence, it is unclear which pancreaticojejunal anastomosis technique is superior (evidence levels 2, 3b, 3c, and 4).
REFERENCES


