Efficacy of Somatostatin and Its Analogues in Prevention of Postoperative Complications After Pancreaticoduodenectomy

A Meta-Analysis of Randomized Controlled Trials

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Objective: The aim of this study was to evaluate the efficacy of somatostatin and its analogues in prevention of postoperative complications after pancreaticoduodenectomy.

Methods: A literature search of the MEDLINE, EMBASE, and Cochrane databases was used to identify randomized controlled trials that compared somatostatin and its analogues with control group after pancreaticoduodenectomy. Meta-analytical techniques were applied to identify differences in outcomes between the 2 groups.

Results: A total of 8 studies were identified according to our inclusion criteria, including 2 studies using somatostatin, 5 studies using octreotide, and 1 study using vapreotide. The use of somatostatin or its analogues did not significantly benefit for reducing the incidence of pancreatic fistula (odds ratio [OR] 95% confidence interval [CI], 0.64–1.37; P = 0.73), total pancreas-specific postoperative complications (OR 95% CI, 0.63–1.42; P = 0.79), delayed gastric emptying (OR 95% CI, 0.50–1.78; P = 0.86), total complication (OR 95% CI, 0.73–1.70; P = 0.61), mortality (OR 95% CI, 0.59–7.72; P = 0.97), and length of postoperative hospital stay (weighted mean difference 95% CI, −7.74 to 4.47; P = 0.60).

Conclusions: The use of somatostatin and its analogues does not significantly reduce postoperative complications after pancreaticoduodenectomy.

Key Words: somatostatin, octreotide, vapreotide, pancreaticoduodenectomy, postoperative complications

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Pancreaticoduodenectomy is a primary surgical procedure for various malignant and benign diseases of the pancreas and periampullary region. Because of progress in surgical techniques and intensive care, the mortality rate after pancreaticoduodenectomy has declined, whereas the morbidity rate remains as high as 28% to 58%.1–4 Pancreatic fistula and other pancreatic stump–related complications are the most common major and formidable problem after pancreaticoduodenectomy. The serious pancreatic fistula may lead to death. Active exocrine secretion of pancreas is considered a major factor responsible for inducing pancreatic fistula, and its inhibition would obviously reduce the incidence and severity of complications after pancreaticoduodenectomy. Numerous methods had been used to manage the complications.

Somatostatin and its analogues are known to have an inhibitory effect on exocrine secretion of pancreas. These drugs had been presumed to reduce the rate of pancreatic fistula. The concept originated in 1979 when Klempa et al5 first reported that somatostatin reduced the incidence of complications after pancreaticoduodenectomy. Since then, many other authors have also evaluated the efficacy of somatostatin in the prevention of postoperative complications after a pancreaticoduodenectomy, but their results have been strongly conflicting. To solve the dispute, we undertook a meta-analysis of all randomized clinical trials that compared somatostatin or its analogues with control group after pancreaticoduodenectomy.

MATERIALS AND METHODS

Inclusion and Exclusion Criteria

Inclusion criteria were established before the search. The randomized controlled trials (RCTs) that evaluated the efficacy of somatostatin or its analogues (octreotide, vapreotide, and lanreotide) in pancreaticoduodenectomy were considered for inclusion. If there were available data about specific pancreaticoduodenectomy subgroups in a mixed pancreatic resection population, then these data were also included in our analysis. The language of the original articles was limited to English. Review articles, retrospective analyses, and abstracts were not included.

Identification of Trials and Search Strategies

The search procedure was performed in duplicate by 2 reviewers. Final inclusion of articles was determined...
by consensus; when this failed, a third author adjudicated. We searched the following medical subject heading terms: *pancreaticoduodenectomy* with the Boolean operator *and*, *somatostatin*, *octreotide*, *vapreotide*, and *lanreotide*. Multiple databases and resources were searched by computer, including MEDLINE (PubMed), EMBASE, and the Cochrane Library. The search was exploded using the “related articles” term in PubMed. Bibliographies and review articles were searched by hand to identify additional studies. A comprehensive hand-based search of reference lists of published articles and review articles was performed to ensure inclusion of all possible studies.

**Data Extraction**

Our 2 reviewers independently extracted data from each matching study using a standardized form. To reduce bias, one of the reviewers was blinded to the source of the publication and to the authors’ names. Inconsistencies between reviewers’ data were resolved through discussion until a consensus was reached. The RCT was scored for quality to assess validity using the Jadad scoring system, which evaluates the studies based on perfect randomization, proper blinding, and an adequate description of withdrawals and dropouts. If the Jadad score of a study is more than or equal to 3, we considered it as a high-quality study. The following data are extracted according to a predefined review form: first author, year of publication, country, number of patients in each arm, study population characteristics, inclusion and exclusion criteria, administration methods of somatostatin or its analogues, anastomotic technique, pathology, definition of pancreatic fistula, number of pancreatic fistulas, morbidity and mortality rates, length of stay, and costs.

**Statistical Analysis**

Meta-analysis was performed according to recommendations from the Cochrane Collaboration and the Quality of Reporting of Meta-analyses guidelines. The effect measures estimated were odds ratio (OR) for dichotomous data and weighted mean difference for continuous data, both reported with 95% confidence intervals (CIs). The OR represents the odds of an adverse event occurring in the somatostatin group compared with the control group. An OR of less than 1 favors the somatostatin group. The point estimate of the OR is considered statistically significant at *P* level of less than 0.05 if the 95% CI does not include the value 1. Studies that contained a zero in 1 cell for the number of events of interest in 1 of the 2 groups resulted in problems with the computation of ratio measurement, so a value of 0.5 was added in both groups from those particular studies.

Heterogeneity was evaluated using the *χ²* test. *P* < 0.1 was considered significant for heterogeneity. Fixed effect models were used throughout, unless statistical heterogeneity was significant, in which case, a random effects model was used.

Analysis was performed using the statistical software Intercooled Stata version 8.2 for Windows (Stata Corporation, College Station, Tex) and Review Manager Version 4.2 (The Cochrane Collaboration, Software Update, Oxford, United Kingdom).

**RESULTS**

The search strategy (Fig. 1) identified 8 randomized trials that met the inclusion criteria. Five is about octreotide versus control group, 2 is about somatostatin versus control group, 1 is about vapreotide versus control group. Outcomes for 1065 patients were examined (Table 1). In all studies (excluding the study of Suc et al in which injection of biological glue into the main pancreatic duct was more often in the octreotide group), the demographics of the 2 groups were all similar including age, sex, pancreatic remnant consistency, diagnostic pathology, anastomotic technique, pylorus preservation, and so on. We will subsequently refer to somatostatin and its analogues as “somatostatin.”

Forest plots were constructed comparing pancreatic fistulas, total pancreas-specific complications, delayed gastric emptying, any complication, mortality, postoperative hospital stay for somatostatin, and its analogues against control group. Heterogeneity between studies was not significant excluding the result of length of stay in hospital (Figs. 2, 3).

**Pancreatic Fistulas**

There was no significant difference between the somatostatins and control group in terms of postoperative pancreatic fistula (OR 95% CI, 0.64–1.37; *P* = 0.73). In addition, the incidence of biochemical and clinical pancreatic fistulas did not differ between the 2 groups.

**Total Pancreas-Specific Complications**

Total pancreas-specific complications were defined as those suggestive of anastomotic disruption including pancreatic fistula, proven anastomotic leak, intra-abdominal collection, and intra-abdominal abscess. There were 4 studies whose data met the definition of total pancreas-specific complications.

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**FIGURE 1.** Search strategy for RCTs comparing somatostatin or its analogues with control group after pancreaticoduodenectomy.
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Jadad Scores</th>
<th>Grouping</th>
<th>Administration Methods</th>
<th>Pancreatic Fistula</th>
<th>Total Pancreas-Specific Complications*</th>
<th>Delayed Gastric Emptying</th>
<th>Any Complication</th>
<th>Mortality</th>
<th>Postoperative Hospital Stay, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hesse et al</td>
<td>2005</td>
<td>Belgium</td>
<td>2</td>
<td>OC group, 41</td>
<td>OC 0.1 mg at the time of incision and 0.1 mg per 8 h for 7 d</td>
<td>12% vs 8%</td>
<td>—</td>
<td>—</td>
<td>2% vs 0%</td>
<td>2% vs 6%</td>
<td>23.12 ± 15.08 vs 20.36 ± 8.07</td>
</tr>
<tr>
<td>Suc et al</td>
<td>2004</td>
<td>France</td>
<td>3</td>
<td>OC group, 92</td>
<td>OC 0.1 mg during the operation and 0.1 mg per 8 h for 10 d</td>
<td>20% vs 21%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>12% vs 6%</td>
<td>—</td>
</tr>
<tr>
<td>Shan et al</td>
<td>2003</td>
<td>Taiwan</td>
<td>3</td>
<td>SOM group, 27</td>
<td>SOM 250 µg/h for 7 d</td>
<td>7% vs 7%</td>
<td>22% vs 48%</td>
<td>40% vs 40%</td>
<td>—</td>
<td>4% vs 4%</td>
<td>28 ± 3.2 vs 30 ± 3.0</td>
</tr>
<tr>
<td>Sarr</td>
<td>2003</td>
<td>United States</td>
<td>1</td>
<td>VAP group, 107</td>
<td>VAP 0.6 mg before operation and twice daily for 7 d</td>
<td>—</td>
<td>27% vs 24%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>27% vs 24%</td>
</tr>
<tr>
<td>Gouillat et al</td>
<td>2001</td>
<td>France</td>
<td>3</td>
<td>SOM group, 27</td>
<td>SOM 6 mg per 24 h (days 1–6) and 3 mg per 24 h (day 7)</td>
<td>11% vs 27%</td>
<td>13% vs 32%</td>
<td>—</td>
<td>21% vs 35%</td>
<td>5% vs 3%</td>
<td>18 ± 1.0 vs 26 ± 2.0</td>
</tr>
<tr>
<td>Yeo et al</td>
<td>2000</td>
<td>United States</td>
<td>5</td>
<td>OC group, 104</td>
<td>OC 150 µg per 8 h for 7 d starting within 2 h postoperation</td>
<td>10% vs 9%</td>
<td>7% vs 10%</td>
<td>40% vs 34%</td>
<td>1% vs 0%</td>
<td>13.3 ± 1.1 vs 11.9 ± 0.6</td>
<td>10% vs 9%</td>
</tr>
<tr>
<td>Lowy et al</td>
<td>1997</td>
<td>United States</td>
<td>1</td>
<td>OC group, 57</td>
<td>OC 150 µg per 8 h for 5 d starting postoperation</td>
<td>28% vs 21%</td>
<td>11% vs 8%</td>
<td>30% vs 25%</td>
<td>2% vs 0%</td>
<td>(Media hospital stay was 15 d in both groups.)</td>
<td></td>
</tr>
<tr>
<td>Montorsi et al</td>
<td>1994</td>
<td>Italy</td>
<td>2</td>
<td>OC group, 76</td>
<td>OC 0.1 mg per 8 h for 7 d starting postoperation</td>
<td>11% vs 15%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>11% vs 15%</td>
</tr>
</tbody>
</table>

*Total pancreas-specific complications were defined as those suggestive of anastomotic disruption including pancreatic fistula, proven anastomotic leak, intra-abdominal collection, and intra-abdominal abscess.
BF indicates biochemical pancreatic fistulas; CF, clinical pancreatic fistulas; OC, octreotide; SOM, somatostatin; VAP, vapreotide.
The incidence of total pancreas-specific complications was not significantly different between somatostatins and control groups after pancreaticoduodenectomy (OR 95% CI, 0.63–1.42; \( P = 0.79 \)).

### Delayed Gastric Emptying and Total Complications

Three studies reported the incidence of delayed gastric emptying. The incidence of delayed gastric emptying was not

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**FIGURE 2.** Forest plot illustrating results of meta-analysis comparing somatostatin or its analogues with control group.
different between somatostatins and control groups after pancreaticoduodenectomy (OR 95% CI, 0.50−1.78; P = 0.86). Similarly, the incidence of total complication was also not different between 2 groups (OR 95% CI, 0.73−1.70; P = 0.61) in 3 studies.

Mortality
Six studies reported the mortality of using somatostatin or its analogues and control group after pancreaticoduodenectomy. Although using somatostatin or its analogues had a tendency to increase the mortality rate, it is without statistical significance (OR 95% CI, 0.90−4.36; P = 0.09).

Postoperative Hospital Stay
Four studies reported the length of postoperative hospital stay. The random effects model meta-analysis did not suggest a significant difference between the 2 groups (weighted mean difference 95% CI, −7.74 to 4.47; P = 0.60).

Publication Bias
A “funnel plot” of the studies in the meta-analysis reporting the incidence of pancreatic fistula and mortality in using somatostatins groups versus control groups is shown in Figures 4 and 5, respectively. This is a scatter plot of the treatment effects estimated from individual studies plotted on the horizontal axis (SE[logES]), against the SE of the estimate shown on the vertical axis (logES). In both figures, all studies lay within the 95% CI and were uniformly distributed around the vertical axis, implying no publication bias. Heterogeneity was not significant between the studies (P = 0.78 and P = 0.92, respectively).

Sensitivity Analysis
We analyzed these studies of using octreotide and somatostatin separately. The incidence of postoperative pancreatic fistula was not different between octreotide control groups in 5 studies (OR 95% CI, 0.73−1.67; P = 0.63) (Fig. 5). There was also no significant difference between somatostatin and control groups (OR 95% CI, 0.15−1.24; P = 0.12) (Fig. 6).

When the studies of low quality (Jadad scores, <3) were excluded, the incidences of pancreatic fistulas, delayed gastric emptying, total complication, mortality, and length of postoperative hospital stays in the remaining 4 studies did not show any significant differences (Fig. 7). The result was same as the above including the studies of low quality.

DISCUSSION
Pancreatic fistula accounts for 8% to 35%4,10,11 of complications after pancreaticoduodenectomy, and once
pancreatic fistula occurs, the associated mortality rate is as high as 9.5% to 40%.\textsuperscript{16,21} Many surgical methods have been developed in an effort to reduce the incidence of postoperative pancreatic fistula including the following: improvements of the pancreatic anastomosis such as the duct-to-mucosa technique, external drainage of the pancreatic duct with an indwelling stent, and the use of fibrin biological glue. However, the efficacy of somatostatin and its analogues in prevention of pancreatic fistula after pancreaticoduodenectomy continues to be disputed.

We searched the articles strictly according to our inclusion and exclusion criteria and got all the articles including the updates. This meta-analysis suggests that there is no significant benefit in terms of administering somatostatin or its analogues in preventing postoperative complications after pancreaticoduodenectomy. Publication bias and sensitivity analysis further confirmed that our results are reliable.

A meta-analysis was performed by Rosenberg et al\textsuperscript{19} in 1997 using data from the 4 European studies\textsuperscript{8,20,22,23} to...
evaluate the efficacy of octreotide in reducing complications and costs in patients undergoing pancreatic resection. The results showed that prophylactic octreotide at the dosage of 3 × 0.1 mg daily had the benefit of reducing complications and costs. However, this meta-analysis relies completely on the European data; these studies included many types of pancreatic resections (pancreaticoduodenectomy, distal pancreatectomy, enucleations, drainage procedures, etc), which confounded the interpretations as fistula rates vary based on the type of resection. In fact, only the study by Montorsi et al specifically distinguished between resectional procedures, stating that octreotide did not decrease fistula rates for pancreaticoduodenectomy (11% octreotide vs 15% control group) but rather only for distal resections (6% octreotide vs 21% control group) and enucleations (0% octreotide vs 57% control group). Furthermore, these studies were financially supported by the makers of octreotide.

The result of meta-analysis by Connor et al. in 2005 showed that somatostatin and its analogues reduced the incidence of complication after pancreatic surgery. In the study by Connor et al., 4 earlier researches included showed that octreotide could significantly decrease the incidence of complication after pancreaticoduodenectomy; however, subsequent researches (6 papers included) did not get the same positive results. As all know, it is completely different between pancreaticoduodenectomy and other pancreatic surgery procedures (such as distal pancreatectomy and local pancreatic resection) in the incidence of pancreatic fistula and other complications. Somatostatin has different effect on different surgery procedures. For example, the study by Montorsi et al demonstrated that octreotide can reduce the incidence of pancreatic fistula after distal pancreatectomy and local pancreatic resection but cannot reduce the incidence of pancreatic fistula after pancreaticoduodenectomy. So we think that the positive result of Connor et al. may be caused by studying a mix of different pancreatic surgical procedures. Furthermore, it is clear that different pancreatic surgical procedures have different indication for pancreatic disease. Thus, the clinical significance of somatostatin and its analogues in whole pancreatic surgery (not to discriminate the subgroups) is poor.

Pancreatic pathology may be associated with pancreatic postoperative complications. It has been reported that prophylactic use of octreotide might have a particular benefit in patients at high risk (patients without chronic pancreatitis) for postoperative complications after pancreatic resection. 20, 23 However, the studies of Yeo et al. 13 and Shan et al. 12 showed that octreotide could not reduce the pancreatic fistula rate and other complications in patients at high risk after pancreaticoduodenectomy. Sue et al. 13 reported that octreotide significantly reduced the rate of intra-abdominal complications after pancreaticoduodenectomy when the main pancreatic duct is less than 3 mm in diameter. Thus, we believe that somatostatin and its analogues are not suitable for conventional applications in pancreaticoduodenectomies involving different pancreas pathology.

The effects of the individual pharmacodynamic actions of the various somatostatins in reducing complications after pancreaticoduodenectomy is also worth attention. Somatostatin, an octapeptide, is more similar with endogenous somatostatin in human body and had an advantage on decreasing the rate of pancreatic fistula as compared with octreotide. For example, in the result of our subgroup analysis, we saw that there was a tendency to increase the rate of pancreatic fistula in somatostatin group. However, a limitation of our subgroup analysis was caused by the size of the group population, which may decrease the significance of our conclusion.

Although the potent inhibitory properties of somatostatin and its analogues may be useful in certain clinical situations, it could be detrimental in others. Many adverse effects are associated with these drugs, such as the need for continuous infusion, painful injection, and gallbladder sludge. After using these drugs, the well-known effect of down-regulation of digestive enzyme secretions could have contributed to the prolonged time to resume intestinal transit and increase delayed gastric emptying. 16 Such down-regulation may also have had negative effect on healing of the anastomosis between small bowel and remnant pancreatic tissue. 25 The mortality rate in treatment group which is higher than that in control group, as shown in our data, may be caused by the adverse effects mentioned previously. Finally, the use of somatostatin or octreotide could not reduce the overall cost of the management of postoperative patients who have undergone pancreaticoduodenectomy. 9 This is especially true in developing countries, where the use of somatostatin or its analogues would increase the cost of treatment significantly. 26

CONCLUSIONS

In conclusion, the results of the current meta-analysis suggest that the use of somatostatin or its analogues should not be routinely recommended for the prevention of postoperative complications associated with pancreaticoduodenectomy. It is urgent to carry out a high-quality RCT study to investigate the efficacy and indication range of somatostatin in prevention of postoperative complications after pancreaticoduodenectomy.

REFERENCES


