Is octreotide beneficial in patients undergoing pancreaticoduodenectomy? Best evidence topic (BET)

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A best evidence topic was written according to a structured protocol. The question addressed was whether the prophylactic administration of somatostatin or somatostatin analogues in patients undergoing pancreaticoduodenectomy (Whipple's procedure) is beneficial in terms of improved surgical outcomes, reduced morbidity or reduced mortality. A total of 118 papers were found using the reported searches of which 5 represented the best evidence (1 meta-analysis, 1 systematic review and 3 randomized control trials). The authors, date, journal, study type, population, main outcome measures and results were tabulated. There is evidence that the perioperative administration of somatostatin or somatostatin analogues reduces biochemical incidence of pancreatic fistula but, it is still unclear if there is a beneficial effect in the incidence of clinically significant pancreatic fistula. Further adequately powered trials with low risk of bias are necessary. From the available data, somatostatin or somatostatin analogues have no effect on mortality post Whipple's. Interestingly, there are only limited data available on the cost-benefit and financial constraints imposed by this treatment, an issue that has only been addressed in a few studies.

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1. Introduction

A best evidence topic (BET) was structured according to the protocol described previously.1,2

2. Clinical problem

In surgical rounds, a patient who has recently undergone a pancreaticoduodenectomy for pancreatic head cancer is presented. The patient had an uneventful post-op course but there is a persistent discharge of an amylase-rich fluid from his drain in post-operative day 10. The patient did not receive prophylactic somatostatin or somatostatin analogues (S/SA). A debate between faculty members is initiated whether the patient should have received prophylactic S/SA and if this treatment is beneficial in patients undergoing Whipple’s. You decide to perform a literature search yourself.

3. Three-part question

In [patients undergoing Whipple’s] is [perioperative prophylactic use of S/SA] beneficial [improved post-operative outcomes]? 

4. Search strategy

Search strategy using Medline from 1980 to July 2012 using the PubMed interface: (pancreatic resection OR pancreatic surgery OR pancreaticoduodenectomy OR pancreatico-jejunostomy OR pancreatico-gastrostomy OR Whipple) AND (octreotide OR somatostatin OR somatostatin analogues) AND (outcome OR mortality OR morbidity OR results OR fistula OR collection OR complication OR hospital stay OR length of stay OR cost OR recovery OR intensive care unit stay). Reference lists of key articles were also manually searched for references. Only articles written in English and involving human subjects were included.

5. Search outcome

One hundred and eighteen articles were retrieved using the above search. Our search retrieved randomized controlled trials (RCTs) and meta-analyses published on this subject in the
Table 1

<table>
<thead>
<tr>
<th>Author, date and country</th>
<th>Patient group (S/SA — somatostatin/somatostatin analogues group, PLC — placebo)</th>
<th>Study type and level of evidence</th>
<th>Outcomes</th>
<th>Key results (S/SA vs. placebo/no treatment)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lai et al.6 2009 China</td>
<td>A systematic review of Randomized Control Trials comparing outcomes of available measures to prevent pancreatic fistula following pancreaticoduodenectomy — specifically for pharmacologic interventions (i.e. S/SA) there were 11 RCTs meeting inclusion criteria</td>
<td>Systematic review (Level 1 evidence)</td>
<td>Pharmacologic interventions (S/SA) Technical interventions</td>
<td>There is evidence level 1 and 2 to support that prophylactic use of S/SA remains controversial. It does not result in decreased mortality. There is need for RCTs with standardization in definition of outcome measurements, treatment regimen, surgical technique and stratification of risk factors</td>
<td>RCTs by, Yeo et al.3 Gouillat et al.4 included. Study by Kolinar et al.5 not available at the time of data extraction</td>
</tr>
<tr>
<td>Gurusamy et al.7 2012 United Kingdom</td>
<td>A systematic review of 19 Randomized Control Trials of peripatheal octreotide in patients undergoing pancreatic surgery</td>
<td>Meta-analysis (Level 1 evidence)</td>
<td>Mortality Drug related complications Post-operative complications Incidence of pancreatic fistula Hospital stay (days) Re-operation rate</td>
<td>Mortality Drug related complications Post-operative complications Incidence of pancreatic fistula Hospital stay (days) Re-operation rate</td>
<td>Most of the trials had a high risk of bias No trial reported on quality of life assessment Definitions of pancreatic fistula not uniform</td>
</tr>
<tr>
<td>Yeo et al.3 2000 USA</td>
<td>Three hundred and eighty three (383) participants — post-randomization drop out 172, sample size 211 (100 females, 111 males), S/SA — 104, PLC — 107 Mean age: 64.7 years Operation performed: pancreaticoduodenectomy in 211 (100%) Pathology: 147 malignancy, 22 chronic pancreatitis Drug and dose: octreotide versus placebo, 250 µg subcutaneously every 8 h for 7 days</td>
<td>PRCT (Level 2 evidence)</td>
<td>Mortality Drug related complications Post-operative complications Incidence of pancreatic fistula Hospital stay (days) Re-operation rate</td>
<td>Mortality Drug related complications Post-operative complications Incidence of pancreatic fistula Hospital stay (days) Re-operation rate</td>
<td>High risk of bias (post-randomization drop out, randomization process, allocation concealment) Pancreatic fistula definition: drainage of &gt;50 ml amylase rich fluid per day (3-fold normal serum levels and over) through drains on or after post-operative day 10, or radiologically demonstrated pancreatic anastomotic disruption One of the studies with the lowest overall fistula reporting Low risk of bias study Pancreatic fistula definition: Drainage of &gt;100 ml/day of amylase rich drainage fluid after day 3, persisting after day 12 or in association with temperature &gt;38 °C or other symptoms requiring surgery, drainage or transfer to intensive care unit</td>
</tr>
<tr>
<td>Gouillat et al.4 2001 France</td>
<td>Seventy five (75) participants (24 females, 40 males) — 8 patients did not complete the study, S/SA — 38, PLC — 37 Mean age 60.2 Operation performed: pancreaticoduodenectomy in 75 (100%) Pathology: 61 malignancy, 4 chronic pancreatitis Drug and dose: Somatostatin versus placebo, continuous infusion for 7 days of 6 mg/24 h somatostatin (days 1–6) and 3 mg/24 h (day 7) or matching placebo (mannitol 4 mg)</td>
<td>PRCT (Level 2 evidence)</td>
<td>Mortality Drug related complications Post-operative complications Incidence of pancreatic fistula Hospital stay (days) Re-operation rate</td>
<td>Mortality Drug related complications Post-operative complications Incidence of pancreatic fistula Hospital stay (days) Re-operation rate</td>
<td>Low risk of bias study Pancreatic fistula definition: Drainage of &gt;100 ml/day of amylase rich drainage fluid after day 3, persisting after day 12 or in association with temperature &gt;38 °C or other symptoms requiring surgery, drainage or transfer to intensive care unit</td>
</tr>
<tr>
<td>Kolinar et al.5 2008 Germany, Switzerland</td>
<td>Sixty seven (67) participants (26 females, 41 males), S/SA — 35, PLC — 32 Mean age: 62.8 years Operation performed: pancreaticoduodenectomy in 67 (100%) Pathology: 33 malignancy, 16 chronic pancreatitis Drug and dose: octreotide versus placebo, 100 µg subcutaneously every 8 h for 7 days</td>
<td>PRCT (Level 2 evidence)</td>
<td>Mortality Drug related complications Post-operative complications Incidence of pancreatic fistula Hospital stay (days) Re-operation rate</td>
<td>Mortality Drug related complications Post-operative complications Incidence of pancreatic fistula Hospital stay (days) Re-operation rate</td>
<td>Low risk of bias Pancreatic fistula definition: output via a drain (surgical or subsequently placed) of any measurable volume of fluid on or after day 3 with an amylase content &gt;3 fold the upper normal serum levels</td>
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</tbody>
</table>

* ns — not significant.
* Possibly related to the drug.
literature, therefore our selection was shortened to publications providing either level 1 on level 2 evidence (22 articles). From these, 5 studies providing the best evidence to answer the clinical question were identified. Two were systematic reviews published recently (2009 and 2012) and three were randomized controlled trials (RCTs). These are presented in Table 1.

6. Results

Three RCTs were included in our BET article. The study by Yeo et al.\(^3\) was the first RCT to address the question by including exclusively patients undergoing a pancreaticoduodenectomy. In total 383 patients were enrolled and randomized. However there was a considerable rate of post-randomization drop-outs in this study (118 patients eventually did not undergo pancreaticoduodenectomy, 14 had a total pancreatectomy and 40 did not receive the minimum of a 5-day course of octreotide), thus allowing a total of 211 patients for analysis. The dosage used was 250 µg of octreotide subcutaneously every eight hours for 7 days. This study had one of the lowest pancreatic fistula rates ever reported in the literature (5% for the placebo group and 11% for the octreotide group). Surgeons performed either a pancreaticojejunostomy or a pancreaticogastrostomy and the two groups were comparable with respect to demographics, type of resection, reported in the literature (9% for the placebo group and 11% for complication rate was 34% in the control group and 40% in the case of pancreaticoduodenectomy. The primary endpoint was the incidence of delayed gastric emptying but, a number of other potential complications following pancreaticoduodenectomy were assessed. Similar to the trial by Yeo et al.,\(^3\) the texture of the pancreatic parenchyma was also assessed in this report. Gastric emptying was evaluated by means of a gastric scintigraphy on 7th post-operative day. There were no differences between the two groups in any of the primary or secondary endpoints. The authors concluded that prophylactic administration of octreotide in patients undergoing pancreaticoduodenectomy should be avoided.

Lai et al.\(^6\) published a systematic review on measures to prevent pancreatic fistula following pancreaticoduodenectomy that preceded the most recent meta-analyses by Gurusamy et al.\(^7\) by three years. This systematic review included the above RCTs except the one reported by Kollmar et al.\(^5\) which was published at the same time of data search. The review concludes that the use of octreotide to prevent pancreatic fistula remains controversial but there is strong evidence that octreotide does not reduce mortality. The available evidence qualifies as level 1 and 2. The identified reasons for these findings are poor pooling of data from RCTs and heterogeneity of the available studies for endpoint measures, definition of outcome measures, treatment regimes, pathologic findings, types of pancreatic surgery and anastomotic technique.

Most recently, Gurusamy et al.\(^7\) published an updated meta-analysis on this subject, including a total of 19 RCTs. In this review, the initial attempt was to evaluate the benefits from the administration of octreotide in both distal and proximal pancreatic surgery and to subsequently perform a subgroup analysis. All the RCTs presented here were part of this analysis and were of the ones that received the highest score in the methodological quality assessment. Out of 19 trials, 17 were classified as having a high risk of bias with the reports by Gouillat et al.\(^4\) and Kollmar et al.\(^5\) being the two with the lowest risk. In total, 2245 patients were analysed. There were no differences in the perioperative mortality or in the number of patients with drug-related adverse effects between the two groups. The overall number of patients with post-operative complications was significantly lower in the S/SA group (RR 0.69; 95% CI 0.58–2.70; \(N = 687\)), however there were no differences in re-operation rate or hospital stay. The incidence of pancreatic fistula was lower in the S/SA group (RR 0.63; 95% CI 0.52–0.77; \(N = 2161\)), although very few trials reported on the proportion of these fistulas that were clinically significant. In the subgroup analysis of those reporting on clinically significant fistulas, there was no difference between the two groups. The authors concluded that there is need for further adequately powered trials having low risk of bias to address the question of whether the use of prophylactic octreotide is beneficial. Based on the current available evidence S/SA are recommended for routine use in patients undergoing pancreatic surgery. It should be outlined however, that a subgroup analysis on different procedures (i.e. distal pancreatectomy and, pancreaticoduodenectomy) was not performed. This was because there were only two trials (the ones by Gouillat et al.\(^4\) and Kollmar et al.\(^5\)) that proved to have a low risk of bias in the sensitivity analysis. Therefore, results from this review need to be interpreted with caution when the issue is pancreaticoduodenectomy rather than pancreatic surgery in general.
7. Clinical bottom line

The administration of S/SA in pancreaticoduodenectomy remains controversial, however it seems from the published literature that a clear benefit is difficult to show. There are very few studies that have approached the issue and have a low risk of bias. Furthermore, there are even fewer studies that have specifically addressed certain subgroups of patients (soft versus hard texture, malignant versus benign disease). Finally it seems that when comparing data from different studies, distal and proximal pancreatic surgery needs to be considered separately. There is a need for further adequately powered, well designed RCTs before definitive conclusions can be drawn. In the meantime, current evidence supports that there is no decrease in the rate of pancreatic fistulas following octreotide administration in pancreaticoduodenectomies and therefore, octreotide should not be administered routinely.

Ethical approval

This is a review article (Best Evidence Topic) and no ethical approval required.

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Author contribution

P Drymousis: data collection, analysis and write up: main author.

M Pai: data collection, manuscript editing.
D Spalding: manuscript editing, direction of investigation.
L R Jiao: manuscript editing, direction of investigation.
N Habib: manuscript review and supervision.
E Zacharakis: study design, manuscript review and supervision.

Conflict of interest

None.

References