Somatostatin and gabexate for post-endoscopic retrograde cholangiopancreatography pancreatitis prevention: meta-analysis of randomized placebo-controlled trials

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CRD summary
This review assessed the effectiveness of somatostatin and gabexate in endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis prevention, concluding that bolus somatostatin, and somatostatin or gabexate administered as an infusion for 12 hours may be effective in post-ERCP pancreatitis prevention. The authors appear to have considered the limitations of the studies and their conclusions are likely to be reliable.

Authors' objectives
To assess the effectiveness of somatostatin and gabexate in the prevention of pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP).

Searching
PubMed (1966 to July 2006), EMBASE (1980 to July 2006) and the Cochrane Library (Issue 2, 2006) were searched. In addition, manual searches were conducted using references of original publications. Publications were restricted to those in English, and the search terms were reported.

Study selection
The included studies involved participants undergoing diagnostic or therapeutic procedures, with or without a history of gallstone or post-ERCP pancreatitis, suspected sphincter of oddi dysfunction, or non-dilated bile duct. The exclusion criteria for participants in the studies were varied, but included patients with the following conditions: acute or chronic pancreatitis or hyperamylasemia, acute cardiac disease, chronic renal disease, diabetes mellitus, medication allergy or using pancreatotoxic medications, prior ERCP or prior post-ERCP pancreatitis, ampullary or biliary malignancy, prior sphincterotomy, or potentially pregnant.

Studies were eligible for inclusion if a minimum dose of somatostatin at 4 μg/kg or 250 μg, or 500 mg gabexate mesylate, was administered as a bolus immediately prior to catheter insertion, or as a continuous infusion 30 to 90 minutes prior to the procedure. The included studies compared controls with patients receiving a dose of somatostatin at 4 μg/kg or 250 μg bolus or 115 to 300 μg/hour continuous infusion for 2.5 to 12 hours, or a continuous infusion of 500 or 1,000 mg gabexate for 2.5 to 12 hours.

Studies were eligible for inclusion if they reported post-procedural pancreatitis rates and post-procedural hyperamylasemia for intervention and control participants. Post-procedural pancreatitis was defined as the occurrence of abdominal pain associated with an increase in amylase levels to three- to five-fold the upper normal limit or greater following the procedure. Post-procedural hyperamylasemia was defined as the occurrence of an isolated elevation of amylase levels to one- to two-fold the upper normal limit or greater. Studies were required to have a minimum follow-up of 24 hours' clinical monitoring and 4 to 6 hours' monitoring of amylase levels post-procedure.

The included studies were double-blind, randomised controlled trials (RCTs).

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Methodological quality was assessed according to the Jadad checklist, which included items on randomisation, concealment and attrition rates. An overall score was assigned to each included study. The authors did not provide details on how the checklist criteria were applied or how many reviewers were involved.

Data extraction
For the main analysis, data were extracted on pancreatitis and hyperamylasemia post-procedural rates, ultimately to
calculate risk differences with 95% confidence intervals (CIs) and relative risk reductions (RRRs). The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

**Methods of synthesis**

Risk differences were pooled using a random-effects model, weighted by the inverse of the variance. The studies were grouped by treatment type duration, and method of administration. Poisson regression analysis was used to test the homogeneity of treatment effects between studies by comparing rates of post-procedural pancreatitis in controls for each drug.

**Results of the review**

Seven double-blinded RCTs (reported as n=3,130; 1,092 receiving somatostatin, 786 gabexate and 1,252 placebo) were included in the main analysis; the sample sizes ranged from 160 to 776 participants. The included RCTs met between four and five of the Jadad validity criteria, with 4 studies meeting all five.

**Somatostatin.**

Significant risk differences in rates of pancreatitis and hyperamylasemia were reported in participants receiving bolus somatostatin or an infusion for 12 hours or more: 8.2% (95% confidence interval, CI: 4.4, 12.0, p<0.0001) and 7.7% (95% CI: 3.4, 12.0, p<0.0001) respectively for pancreatitis, representing RRRs of 73.7% and 75.8%, and 12.1% (95% CI: 4.8, 19.4, p=0.001) and 11.0% (95% CI: 2.0, 20.1, p=0.017) respectively for hyperamylasemia. For pancreatitis outcome, the number-needed-to-treat (NNT) was 13 in the group receiving bolus and 12 in the group receiving infusion for 12 hours or more. No significant risk differences in rates of pancreatitis or hyperamylasemia were reported for participants receiving an infusion for less than 12 hours. Significant overall risk reductions were reported for pancreatitis: 2.9% (95% CI: 0.9, 4.9, p=0.005) and hyperamylasemia 5.2% (95% CI: -1.8, 8.5, p=0.003).

**Gabexate.**

Significant risk differences in pancreatitis rates were reported in participants receiving an infusion for 12 hours or more: 5.2% (95% CI: 1.1, 9.4, p=0.01), representing an RRR of 68.4%. The NNT for this group was 20. No significant risk differences were reported for participants receiving an infusion for less than 12 hours, or for overall risk difference across groups. No significant risk differences in rates of hyperamylasemia were reported.

No significant differences were observed in rates of pancreatitis for controls.

In addition to the 7 RCTs used in the main analysis, 7 additional placebo-controlled randomised trials, which did not meet the predetermined study protocols defined by the authors, were included in the ancillary analysis; the results were reported in the review.

**Authors' conclusions**

Somatostatin administered as a bolus may be effective in reducing post-ERCP rates of pancreatitis and hyperamylasemia, and somatostatin or gabexate administered as an infusion for 12 hours may be effective in the prevention of post-ERCP pancreatitis, but further research is required.

**CRD commentary**

The review question was clear and was supported by appropriate inclusion criteria for the interventions and outcomes. Relevant literature searches were undertaken using electronic databases and other appropriate sources. However, restrictions on language of publication might have introduced language bias. Together with the fact that there was no apparent search for unpublished material, it is possible that relevant papers were missed. An assessment of publication bias was not reported. Validity was assessed according to published criteria. However, details of the methods used to select studies, assess validity and extract the data were not reported, which means that the potential for reviewer error and bias cannot be ruled out. Although some details were reported clearly, potentially important clinical information on participant characteristics and details of control treatments were not reported. Despite some assessment of homogeneity, the lack of reporting of study characteristics makes it difficult to judge the appropriateness of pooling, and wide CIs tend to indicate that there may be a problem. In addition, sample sizes were small. The authors appear to have considered certain limitations with the included studies, and their conclusions are therefore likely to be reliable.
but further research is required.

**Implications of the review for practice and research**

Practice: The authors stated that there are concerns about the efficacy of gabexate and recommended avoiding its use in the prevention of post-ERCP pancreatitis. They also stated that the most effective method for administering somatostatin in high-risk patients not suitable for alternative studies is as a bolus, using doses of 4 μg/kg or 250 μg.

Research: The authors stated that large, high-quality placebo-controlled and randomised studies are required to compare high-risk patients receiving placebo, somatostatin as a bolus, and somatostatin as a bolus followed by 4 to 6 hours' infusion.

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the reliability of the review and the conclusions drawn.