Prophylactic pancreatic stent placement and post-ERCP pancreatitis: a systematic review and meta-analysis

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CRD summary
The review concluded that pancreatic stent placement after endoscopic retrograde cholangiopancreatography (ERCP) reduced the risk of post-ERCP pancreatitis in adults. Lack of reported review process, limitations in the analyses and uncertain study quality mean that the reliability of the authors' conclusion is unclear.

Authors' objectives
To determine the efficacy and safety of pancreatic stent placement for the prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis.

Searching
MEDLINE, ProQuest 5000 and The Cochrane Library were searched from January 1974 to December 2009; search terms were reported. Conference abstracts from American Gastroenterological Association, American College of Gastroenterology, American Society of Gastrointestinal Endoscopy and United European Gastroenterology Week were searched from 2002 through 2009. Bibliographic reviews were searched manually. No formal inquiry was made to pharmaceutical companies. A further search of MEDLINE and ProQuest 5000 was made from 1991 to 2010, in addition to handsearching, for immediate adverse events. Only articles published in English were accepted.

Study selection
Randomised controlled trials (RCTs) for prevention of post-ERCP pancreatitis (PEP) in adults were eligible for inclusion if they compared pancreatic stent placement after ERCP with no stent placement after ERCP. Studies were required to report relative risks (RRs) or provide sufficient data for their calculation. The primary outcome was development of PEP. Secondary outcomes included incidence of immediate adverse events (such as infection, bleeding, cholangitis or cholecystitis, pancreatic necrosis, pancreatic stent migration or occlusion, duct perforation, pseudocyst and retroperitoneal perforation). Due to insufficient data from RCTs, observational studies were also sought for the assessment of adverse events. Studies that involved wire-guided cannulation or pharmacoprophylaxis, studies with technical problems (undefined) and studies from developing countries were excluded.

Therapeutic interventions (biliary sphincterotomy, pancreatic sphincterotomy and precut papillotomy), indications for ERCP, administration of sedation and protease inhibitors and prophylactic antibiotic use varied across the included studies. Pancreatic stents varied in material, design and configuration: single or double flanged, 5Fr to 7Fr diameter and 2cm to 5cm long. The stent was removed endoscopically in most trials and was spontaneously dislodged in two trials. Duration of placement ranged from one to 14 days after ERCP. Definition of PEP varied across studies. In most trials severity of PEP was graded as mild, moderate or severe according to the criteria of Cotton et al. All trials included high-risk groups (such as sphincter of Oddi dysfunction, difficult cannulation, sphincterotomy, pancreatic sphincterotomy, biliary balloon dilation of intact papilla for stone extraction, endoscopic ampullectomy and pancreatic brush cytology). Mean age ranged from 46 to 66 years in the stent group and 44 to 69 years in the control group. The proportion of female participants ranged from 31% to 94%. All trials were conducted in USA or Japan.

The authors did not state how many authors performed study selection.

Assessment of study quality
The quality of the RCTs was assessed using criteria of allocation concealment, double-blinding of outcome assessment and handling of withdrawals (intention-to-treat).

The authors did not state how many reviewers assessed study quality.
Data extraction
Relative risks (or data that enabled calculation of relative risks) were extracted on an intention-to-treat basis for development of PEP. Rate of immediate adverse events was recorded for each study. Authors of the included studies were contacted for additional data where required.

The authors did not state how many reviewers were involved in data extraction.

Methods of synthesis
Where there was no significant heterogeneity, pooled relative risks and associated 95% confidence intervals (CIs) were calculated using a fixed-effect model. A random-effects model (restricted maximum likelihood method) was performed where significant heterogeneity was found. A non-comparative descriptive index was calculated (after logarithmic transformation of the proportions) for immediate adverse events and a pooled weighted estimate of immediate adverse events with 95% CIs was calculated (inverse variance model). Statistical heterogeneity was assessed using Cochran's $Q$ and $I^2$. Subgroup analyses were carried out, stratifying by severity of pancreatitis and patient selection (high-risk patients and mixed-case groups). Sensitivity analyses were performed by removing one study at a time from each analysis. Meta-regression was used to explore potential causes of heterogeneity.

Results of the review
Eight RCTs (n=671 participants) were included in the main meta-analyses. Five RCTs described the randomisation method. One RCT reported intention-to-treat analysis. No RCTs were double-blinded. The adverse events analyses included 17 studies (n=4,115): 15 observational studies and two RCTs.

Pancreatic stent placement was associated with a statistically significant reduction in PEP compared with no stent placement (RR 0.32, 95% CI 0.19 to 0.52, $I^2$=0%; eight RCTs).

Subgroup analyses stratified by pancreatic severity showed a similar reduction in PEP for mild-moderate pancreatitis (RR, 0.36, 95% CI 0.22 to 0.60, $I^2$=0%; eight RCTs) and severe pancreatitis (RR 0.23, 95% CI 0.06 to 0.91, $I^2$=0%; five RCTs) compared to controls. Subgroup analysis stratifying by patient selection showed a statistically significant reduction in PEP for high-risk (RR 0.35, 95% CI 0.20 to 0.61, $I^2$=0%; six RCTs) and mixed-case groups (RR 0.23 95% CI 0.08 to 0.66, $I^2$=0%; two RCTs).

Sensitivity analyses did not significantly change the results, except for severe PEP (no significant between-group difference was found after exclusion of one study); data were not shown. Univariate meta-regression analysis showed no significant association with methodological criteria (allocation concealment and intention-to-treat analysis) for the primary outcomes.

The pooled weighted estimate of overall complication was 4.4% (95% CI 2.8 to 7.5%, $I^2$= 76%; 17 studies). The most frequent immediate events were occlusion (7.9%, 95% CI 1.7 to 21.4%; one study), pancreatic stent migration (4.9%, 95% CI 2.5 to 9.8%, $I^2$=60.2%; seven studies) and cholangitis and cholecystitis (3.1%, 95% CI 1.2 to 8.1%; three studies).

Authors' conclusions
Pancreatic stent placement after ERCP reduced the risk of PEP compared with no placement and was particularly beneficial for patients at high risk.

CRD commentary
The review question was supported by clear inclusion criteria. Several relevant sources were searched and some attempt was made to locate unpublished articles. The literature search was restricted by language and as such relevant studies may have been missed, which increased the risk of publication bias. Publication bias was not formally assessed due to the small number of included studies. The authors did not report that they used appropriate methods to reduce risks of reviewer bias and error during study selection, data extraction and assessment of study quality. Study quality was assessed using appropriate criteria and individual results were reported. Most studies were observational and the overall quality of the RCTs was not high. It appeared that the main meta-analysis for PEP development may have included control participants who had been counted more than once and this may have affected the results. The meta-analyses of
adverse events combined RCTs and observational studies (not generally recommended). Few incidences for immediate adverse events were observed and most studies were not long term. The authors acknowledged a number of limitations that included heterogeneity, low study quality and small sample size.

Lack of reported review process, limitations in the analyses and uncertain study quality mean that the reliability of the authors' conclusion is unclear.

Implications of the review for practice and research

**Practice**: The authors did not state any implications for practice.

**Research**: The authors stated that well-conducted RCTs with large sample sizes were required to confirm the review findings. Efficacy of pancreatic stents for severe PEP, identification of risk factors and management of adverse effects, optimal timing of stent placement and removal and comparison of pancreatic stenting with wire-guided cannulation or pharmacoprophylaxis all warranted attention.

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