Meta-analysis: nitroglycerin for prevention of post-ERCP pancreatitis
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CRD summary
This review supported nitroglycerin use for the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis, but concluded that dermal administration did not show beneficial effects and required further investigation. The authors’ conclusions appear to reflect the evidence, but given several limitations with the included trials, including insufficient power and potential for bias in the review, the conclusions may not be reliable.

Authors’ objectives
To assess the effectiveness of nitroglycerin for the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis.

Searching
MEDLINE, EMBASE, and the Cochrane Library were searched for relevant articles, and reference lists were handsearched. Search terms were reported. Abstracts published in the annual meetings at Digestive Disease Week and United European Gastroenterology Week were also searched from 2002 to 2008.

Study selection
Randomised and placebo-controlled trials assessing the effect of nitroglycerin for the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis in humans were eligible for inclusion. The primary outcome of interest was the incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis. Secondary outcomes were post-endoscopic retrograde cholangiopancreatography pancreatitis-related mortality and side-effects.

Included trials were of patients over the age of 18 years and were conducted in seven different countries. Patients excluded from the primary trials included those with acute or chronic pancreatitis, hypotension, hypersensitivity to nitrates, and those with previous sphincterotomy. Treatments included sublingual, transdermal, or intravenous nitroglycerin administered at varying doses between five minutes and one hour prior to endoscopic retrograde cholangiopancreatography. The incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis in patients receiving nitroglycerin were compared with the incidence in patients receiving placebo. The definition of post-endoscopic retrograde cholangiopancreatography pancreatitis varied slightly between studies, but included pain and elevated serum amylase.

Two reviewers independently screened papers for inclusion, but it was unclear how discrepancies were resolved.

Assessment of study quality
Study quality was assessed using the following criteria: randomisation, allocation concealment, blinding, follow-up, and intention-to-treat analysis. Use of co-intervention for each treatment group was also assessed.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
Two reviewers extracted data on the incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis and side-effects to calculate relative risks (RRs) with their 95% confidence intervals (CIs). Where trial details were unclear, authors were contacted for further information. Discrepancies were resolved through referral to a third reviewer.

Methods of synthesis
Both fixed-effect and random-effects models were used to combine relative risks with their 95% confidence intervals. Statistical heterogeneity was assessed using the X² and I² tests. Sensitivity analyses were performed to include only RCTs administering nitroglycerin by dermal patch for the primary outcome, and by excluding trials using intravenous
nitroglycerin with general anaesthesia for side-effects. Intention-to-treat analysis was also conducted using both best-case and worst-case scenarios.

Results of the review
Five randomised controlled trials (RCTs) were included in the review (n=1,660 patients). Sample sizes ranged between 142 and 806 patients. All RCTs reported randomisation methods and were double-blind. Where reported, treatment groups received equal co-intervention. Only one RCT reported complete follow-up, with the remaining RCTs reporting between 1% and 10% of patients lost to follow-up. None of the RCTs used intention-to-treat analyses. Follow-up ranged between 24 hours and one month.

There were significantly fewer incidences of post-endoscopic retrograde cholangiopancreatography pancreatitis in patients receiving nitroglycerin compared to the placebo group (RR 0.62, 95% CI 0.43 to 0.90; five RCTs; random-effects model). Sensitivity analysis including only RCTs administering nitroglycerin as a dermal patch showed no statistically significant difference between intervention group and placebo group (three RCTs). There was no evidence of statistical heterogeneity.

There was a statistically significant increase in hypotension (RR 2.25, 95% CI 1.71 to 2.96; three RCTs) and headaches (RR 3.64, 95% CI 1.79 to 7.40; four RCTs) in patients receiving nitroglycerin, and this was supported by sensitivity analysis. There were no significant differences for mortality (two RCTs).

Intention-to-treat analysis was reported in the review.

Authors’ conclusions
The evidence supported the use of nitroglycerin for the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis. However, the preferred route of administration using dermal route did not show beneficial effects and requires further investigation.

CRD commentary
The review question was clear and was supported by appropriate inclusion criteria for study design, intervention, outcomes, and broad criteria for participants. Appropriate sources were used to search for relevant literature, although the search dates were limited to between four and six years. Attempts were made to locate abstracts, which reduced the possibility that potentially relevant papers were missed. However, it was unclear whether non-English papers were eligible for inclusion, which meant that language bias could not be ruled out. Validity was assessed using appropriate criteria, and quality appeared adequate. Certain steps were taken to reduce the potential for reviewer error and bias by undertaking study selection and data extraction in duplicate, but not for validity assessment. Appropriate methods were used to combine the trials and assess for statistical heterogeneity. The authors suggested that populations were comparable for age and gender, but no other participant characteristics were detailed. Methods of treatment administration varied among trials, and follow-up duration was short. The authors acknowledged certain limitations with the included trials, such as high drop-out rates in some of the RCTs, and insufficient power due to insufficient sample sizes. Confidence intervals were wide for some comparisons. Although the authors’ conclusions appear to reflect the evidence, they should be interpreted with caution given the limitations mentioned.

Implications of the review for practice and research
Practice: The authors stated that patients receiving nitroglycerin delivered by a dermal patch prior to endoscopic retrograde cholangiopancreatography should be monitored for hypotension up to one hour after removal of dermal patch.

Research: The authors stated that further multi-centre studies are required to achieve sufficiently powered studies, and that further studies are warranted to investigate the use of nitroglycerin administered through the dermal route.

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