
Nitroglycerin in the prevention of post-ERCP pancreatitis: a meta-analysis

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CRD summary

This well-conducted review concluded that, based on the limitations of the meta-analysis, prophylactic use of nitroglycerin for all patients that undergo endoscopic retrograde cholangiopancreatography was not recommended. These conclusions are likely to be reliable.

Authors' objectives

To evaluate the effect of prophylactic nitroglycerin in the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis.

Searching

PubMed, EMBASE, the Cochrane Library and Science Citation Index were searched for studies in any language (dates spanned 1966 to 2008). Search terms were reported. The 2006 to 2008 proceedings of the American Gastroenterological Digestive Disease week and the United European Gastroenterology week and reference lists of retrieved studies were also searched.

Study selection

Randomised controlled trials (RCTs) that compared prophylactic nitroglycerin (regardless of initial time of treatment, duration, dose and route of administration) with placebo in patients receiving endoscopic retrograde cholangiopancreatography were eligible for inclusion. Eligible trials had to report the incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis

The included trials were conducted in the UK, Spain, Australia and France. The delivery of nitroglycerin varied between includes trials; oral, transdermal patch and intravenous delivery were described. Most trials used the post-endoscopic retrograde cholangiopancreatography pancreatitis diagnostic criteria proposed by Cotton et al. Three trials were single-centre; the rest were multi-centre. Most trials included patients undergoing diagnostic or therapeutic endoscopic retrograde cholangiopancreatography.

Two reviewers selected studies for inclusion; disagreements were resolved by discussion

Assessment of study quality

Methodological quality was assessed using the Jadad scale (randomization, withdrawals and drop-outs) to give a quality score out of 5 points. Trials that scored at least 3 were considered high quality.

It appeared that two reviewers assessed study quality; disagreements were resolved by two reviewers.

Data extraction

Incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis was extracted independently by two reviewers. Relative risks (RRs) and 95% confidence intervals (CIs) calculated. Data on severity of post-endoscopic retrograde cholangiopancreatography pancreatitis and adverse events were also extracted. Disagreements were resolved by consensus.

Methods of synthesis

Relative risks and 95% confidence intervals were pooled using a fixed-effect meta analysis in the absence of statistical heterogeneity ($p < 0.05$). A random-effects model was used if heterogeneity was present. Heterogeneity was assessed using the χ^2 and I^2 tests.

A sensitivity analysis was performed by excluding a trial in which the diagnostic criteria were not those proposed by Cotton et al.

Subgroup analyses were performed for setting (single or multi-centre) and pre-treatment risk of post-endoscopic retrograde cholangiopancreatography pancreatitis (low, moderate or high).

Publication bias was assessed using Beggs test.

Results of the review

Four RCTs were included in the review (n=856 patients; range 144 to 318). All of the RCTs scored 5 points on the Jadad scale.

Prophylactic nitroglycerin use was significantly associated with a reduction of overall post-endoscopic retrograde cholangiopancreatography pancreatitis (RR 0.60, 95% CI 0.39 to 0.92; 856 patients). The incidence of moderate or severe post-endoscopic retrograde cholangiopancreatography pancreatitis was not significantly reduced by nitroglycerin. There was no significant heterogeneity in the analyses.

Sensitivity analysis, excluding a trial in which diagnostic criteria were not proposed by Cotton et al, found that there was no longer any significant difference between treatment and placebo. The sensitivity analysis for severity of post-endoscopic retrograde cholangiopancreatography pancreatitis was not changed as there were no moderate or severe patients in the excluded trial.

Subgroup analyses of single centre trials (RR 0.58, 95% CI 0.35 to 0.97; 648 patients) or trials with low risk of post-endoscopic retrograde cholangiopancreatography pancreatitis (RR 0.38, 95% CI 0.19 to 0.75; 330 patients) supported the prophylactic effect of nitroglycerin on overall post-endoscopic retrograde cholangiopancreatography pancreatitis. Multi-centre trials or trials with moderate to high risk of post-endoscopic retrograde cholangiopancreatography pancreatitis did not demonstrate a significant difference between nitroglycerin and placebo. There was no significant effect of nitroglycerin in the prevention of moderate or severe post-endoscopic retrograde cholangiopancreatography pancreatitis in any of the subgroup analyses.

Hypotension and headache were the main adverse effects.

Authors' conclusions

Based on the limitations of this meta-analysis, prophylactic use of nitroglycerin for all patients that undergo endoscopic retrograde cholangiopancreatography was not recommended.

CRD commentary

The inclusion criteria were clearly stated. A number of relevant databases were searched in all languages, reducing the risk of language bias. It did not appear that unpublished studies were sought, so publication bias may have been possible. A funnel plot was included to assess publication bias, but the small number of included trials meant this may have not been reliable. The review processes were performed in duplicate, reducing the risk of reviewer error and bias.

Trial quality was assessed and taken into consideration. Meta-analysis appeared appropriate. The authors acknowledged the limitations of the included trials.

This was a well-conducted review and the authors' conclusions are likely to be reliable.

Implications of the review for practice and research

Practice: The authors stated that compared with intravenous administration, sublingual or transdermal delivery of nitroglycerin might be safer, well-tolerated and easier to administer. Based on the limitations of this meta-analysis prophylactic use of nitroglycerin for all patients that undergo endoscopic retrograde cholangiopancreatography is not recommended.

Research: The authors stated that further well-designed placebo controlled trials are required to confirm the effect of nitroglycerin in preventing post-endoscopic retrograde cholangiopancreatography pancreatitis. The authors recommended that: trials should be multi-centre or large single-centre studies; details of procedure- and patient-related

incidences of post-endoscopic retrograde cholangiopancreatography pancreatitis and other complications should be recorded; high risk patients should be enrolled; nitroglycerin should be administered in the sublingual or transdermal way; dose ranging studies are needed; and sample sizes must be sufficient to detect significant differences.

Funding

Not stated.

Bibliographic details

Shao LM, Chen QY, Chen MY, Cai JT. Nitroglycerin in the prevention of post-ERCP pancreatitis: a meta-analysis. *Digestive Diseases and Sciences* 2010; 55(1): 1-7

PubMedID

19160042

DOI

10.1007/s10620-008-0709-9

Original Paper URL

<http://www.springerlink.com/content/6r131003r16645k3/>

Indexing Status

Subject indexing assigned by NLM

MeSH

Cholangiopancreatography, Endoscopic Retrograde /adverse effects; Humans; Nitroglycerin /adverse effects /therapeutic use; Pancreatitis /etiology /prevention & control; Randomized Controlled Trials as Topic; Sphincter of Oddi /drug effects

AccessionNumber

12010000668

Date bibliographic record published

14/04/2010

Date abstract record published

27/04/2011

Record Status

This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.