Role of nonsteroidal anti-inflammatory drugs in the prevention of post-ERCP pancreatitis: a meta-analysis

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CRD summary
The authors' concluded that the prophylactic use of non-steroidal anti-inflammatory drugs can reduce the incidence of pancreatitis after endoscopic retrograde cholangiopancreatography. Given some concerns about the reporting of the review process, the extent to which the authors' conclusions can be relied upon is unclear.

Authors' objectives
To evaluate the effectiveness of non-steroidal anti-inflammatory drugs to prevent pancreatitis after endoscopic retrograde cholangiopancreatography.

Searching
PubMed and EMBASE were searched from 1980, and the Cochrane Library was searched (Issue 2, 2008) to identify published studies for inclusion in the review. Search terms were reported. The bibliographies of relevant studies and recent review articles were scanned for additional material of interest.

Study selection
Randomised placebo-controlled trials (RCTs) of non-steroidal anti-inflammatory drugs administered to prevent pancreatitis in patients at risk following endoscopic retrograde cholangiopancreatography were eligible for inclusion in the review. The primary outcomes of interest were incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis, serum amylase values, non-steroidal anti-inflammatory drug-associated side effects, length of hospital stay, and hospital mortality. Review articles, retrospective analyses, case reports, and abstracts were excluded.

The included participants comprised men and women with a mean age range of 45 to 60 years receiving diclofenac, indomethacin, or placebo. Some had a history of pancreatitis or had bile duct stones.

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

Assessment of study quality
Trial quality assessment was assessed on aspects of randomisation, blinding and withdrawals using the Jadad scale. Trials with a Jadad score less than or equal to 2 were deemed low quality, and scores greater than or equal to 3 were considered to be high quality. Allocation concealment was assessed (yes; no; unclear) using Cochrane Collaboration criteria.

The authors did not state how the validity assessment was performed.

Data extraction
Two independent reviewers extracted the primary outcome data in order to present odds ratios or mean differences and 95% confidence intervals. Data were also extracted on the details of the endoscopic retrograde cholangiopancreatography procedures (number of cannulations and pancreatic duct injections, and whether a sphincterotomy was performed); the dose, frequency, duration, and formulation of drugs (enema, suppository, or foam); and any adverse effects of treatment. Authors were contacted for missing data, where necessary.

Methods of synthesis
Odds ratios were pooled, and mean differences were weighted and pooled in meta-analyses. Statistical heterogeneity was assessed using the $X^2$ and $I^2$ statistics. Where the $I^2$ statistic was less than or equal to 50%, a fixed-effect meta-analysis was conducted; otherwise, a random-effects model was employed. Where clinical heterogeneity was detected (regarding study population and treatments), the results were synthesised narratively and differences were explored in
sub-group analyses.

**Results of the review**

Six randomised controlled (RCTs) were included in the review (n=1,300 participants). Placebo was given to 648 participants; and 652 participants received non-steroidal anti-inflammatory drugs (271 received diclofenac, 381 received indomethacin). Four trials were double-blind and achieved a Jadad score of five; the remaining two trials received a score of two.

When compared to placebo, the risk of pancreatitis was significantly lower in patients who received non-steroidal anti-inflammatory drugs, odds ratio 0.46 (95% confidence interval (CI): 0.32 to 0.65; six trials). The mean serum amylase level two hours after endoscopic retrograde cholangiopancreatography was significantly lower in patients who received non-steroidal anti-inflammatory drugs compared to placebo, weighted mean difference -91.09 (95% CI: -149.78 to -32.40; four trials). There was no significant heterogeneity in either analysis. There was no difference in mean serum amylase between the groups at 24 hours post procedure, and significant heterogeneity was reported (p=0.04; two trials).

In sub-group analyses, one trial (n=220 participants) found that diclofenac was significantly more effective than placebo in patients who had sphincterotomy (p=0.021) and in those without sphincter of Oddi hypertension (p=0.036). A further trial (n=442 participants) found that indomethacin was significantly more effective than placebo in patients with pancreatic duct injection (p=0.014).

None of the trials reported adverse effects from one or two doses of non-steroidal anti-inflammatory drugs.

**Authors’ conclusions**

The prophylactic use of non-steroidal anti-inflammatory drugs can reduce the incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis.

**CRD commentary**

This review addressed a clear question and the inclusion criteria were potentially reproducible for aspects of study design, participants, interventions and outcomes. The search strategy included relevant sources, but the restriction to published studies may mean that some data were missed, and publication bias could not be ruled out. An appropriate validity assessment was carried out, and the results of this were used in the presentation of results. Trial details were adequately provided, and the methods of synthesis appeared to be appropriate. Data extraction was carried out with sufficient measures to minimise error and bias. However, the processes of study selection and validity assessment were not reported, and this may represent limitations to the reliability of the review. The authors highlighted further potential limitations imposed by the inclusion of small sample sizes of high risk individuals, the absence of follow-up to fully evaluate the safety of non-steroidal anti-inflammatory drugs, and clinical variation in terms of endoscopic retrograde cholangiopancreatography procedures and pharmacological regimens. Given some concerns about the reporting of review process, the extent to which the authors’ conclusions can be relied upon is unclear. Worthy of note is the discrepancy of reporting in the paper, where routine use of prophylactic non-steroidal anti-inflammatory drugs in patients undergoing endoscopic retrograde cholangiopancreatography is recommended by the authors in the results section of the paper, but is clearly not recommended for routine use in the abstract.

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

**Practice:** The authors stated that the prophylactic administration of non-steroidal anti-inflammatory drugs is recommended in patients undergoing endoscopic retrograde cholangiopancreatography, but not as routine care.

**Research:** The authors stated that larger, more rigorous, double-blind randomised controlled trials are needed to explore the effects of other anti-inflammatory agents, or combinations of drugs with various inhibitory effects on inflammatory pathways. A larger study of patients undergoing pancreatic duct injection is needed to further investigate the efficacy of non-steroidal anti-inflammatory drugs.

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