Cyclooxygenase-2 inhibitors in postoperative pain management: current evidence and future directions

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CRD summary
This review assessed the use of cyclooxygenase-2 (COX-2) inhibitors for pain following surgery. In terms of pain reduction and side-effects, the authors concluded that COX-2 inhibitors are similar to non-steroidal anti-inflammatory drugs. The review does not give enough information to enable a confident judgement about how reliable or generalisable the conclusion is.

Authors' objectives
To examine the role of cyclooxygenase-2 (COX-2) inhibitors in the management of post-operative pain.

Searching
MEDLINE (from 1966 to 2003) and the Cochrane Controlled Trials Register (Issue 3, 2002) were searched; the search terms were reported. Study reports that were only available as abstracts were not included in the review.

Study selection
Study designs of evaluations included in the review
Double-blind, randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies that compared a COX-2 inhibitor with placebo were eligible for inclusion. This included studies that had an active control group such as a non-selective non-steroidal anti-inflammatory drug (NSAID), acetaminophen (paracetamol) or opioid, as well as a placebo group. The COX-2 inhibitors used in the included studies were oral rofecoxib, celecoxib, valdecoxib, nimesulide, rectal meloxicam, and intramuscular or intravenous parecoxib. The doses varied: most of the included trials used a single dose while some used multiple doses. In most trials the intervention was given post-operatively. In a few trials the COX-2 inhibitor was given together with acetaminophen, which was also given to the control groups. Active comparator treatments included diclofenac, ibuprofen, naproxen, ketorolac, niflumic acid, morphine, and hydrocodone or codeine plus acetaminophen.

Participants included in the review
Inclusion criteria for the participants were not stated. The types of surgery in the included trials were described as oral, lumbar disc, spinal fusion, major or ambulatory orthopaedic, total knee or hip arthroplasty, arthroscopic meniscectomy, prostatectomy, hysterectomy, tonsillectomy, and ear, nose and throat.

Outcomes assessed in the review
Inclusion criteria for the outcomes were not stated. The main outcome used in the review was analgesic efficacy. The studies included in the review used measures of efficacy such as analgesic use, pain relief and pain intensity. Side-effects were also reviewed. The studies included in the review assessed adverse effects by several means, including spontaneous patient reporting, physical examination, laboratory tests, blood loss, and nausea and vomiting.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The validity of the included studies was not assessed beyond restricting inclusion to double-blind RCTs. The authors did not state how the papers were assessed for validity, or how many reviewers performed the validity assessment.
**Data extraction**

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The actual outcome data extracted from each trial to represent analgesic efficacy was not stated. The approach used to extract data on adverse effects was not reported.

**Methods of synthesis**

**How were the studies combined?**

For analgesic efficacy, the studies were combined as a tally of the number of trials that showed a statistically significant difference between the treatment and control and the number that showed no difference. If a study used several measures of analgesic efficacy that did not all show a difference between the treatment and control, the outcome that did show a difference was used in the review. The studies were grouped by the particular COX-2 inhibitor compared with placebo, and by comparisons with active controls and comparisons between different COX-2 inhibitors. A narrative summary was used for dose-response, safety and side-effects.

**How were differences between studies investigated?**

Differences between the studies were not investigated.

**Results of the review**

Thirty-two trials (n=6,413) were included.

Seventeen trials showed that rofecoxib had superior analgesic efficacy compared with placebo, while two showed no difference. Five trials showed that celecoxib had superior analgesic efficacy compared with placebo, while one showed no difference. Superior analgesic efficacy to placebo was reported in all trials of parecoxib (5 trials) valdecoxib (3 trials), nimesulide (1 trial) and meloxicam (1 trial).

Thirteen of the 17 comparisons of COX-2 inhibitors with non-selective NSAIDs and one of the 3 comparisons with opioids showed no difference in analgesic efficacy. Two trials compared rofecoxib with celecoxib and showed rofecoxib to be superior. One trial compared rofecoxib with valdecoxib and showed valdecoxib to be superior.

Seven trials that compared different doses of oral rofecoxib suggested that 50 mg gave the best effect and higher doses were not more effective. The results of 5 trials that compared 20- and 40-mg doses of parecoxib were inconsistent; one trial that also studied a dose of 80 mg showed no difference in effect compared with 40 mg. Two trials compared different doses of valdecoxib. One of these showed no difference between 80 and 40 mg, but showed that 40 mg was better than 20 mg, which was better than 10 mg. The other trial showed no difference between 20 and 40 mg. One trial of oral nimesulide showed no difference between 100- and 200-mg doses.

Twenty-three of the 32 included trials assessed adverse effects and the majority reported no difference in overall incidence. Two trials reported significantly more post-dental extraction alveolitis with rofecoxib compared with placebo.

**Authors' conclusions**

COX-2 inhibitors for post-operative pain have similar analgesic efficacy, safety and tolerability to non-selective NSAIDs.

**CRD commentary**

Apart from the study design of interest, the criteria for the inclusion of studies in this review were not clearly set out. The search for studies was not extensive. The authors did not state whether any language restrictions were applied, nor did they mention the possibility of publication bias. The quality of the included studies was not fully appraised. A lack of information means that an assessment of the potential for bias in the conduct of the review is not possible. The non-transparent way in which the individual study findings were presented, and the use of tallies to synthesise the data, raises concerns about the reliability and generalisability of the review's conclusions.
Implications of the review for practice and research

Practice: The authors stated that, in the absence of strong evidence supporting any major advantage of COX-2 inhibitors, cost-benefit considerations are likely to guide the choice of therapy.

Research: The authors stated that studies are needed to compare COX-2 inhibitors and non-selective NSAIDs with respect to gastric, renal and coagulation problems, cardiovascular outcomes, and post-operative recovery and physiologic impairment.

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