The role of COX-2 inhibitors in the perioperative setting: efficacy and safety. A systematic review
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CRD summary
The author concluded that selective cyclooxygenase-2 inhibitors may be effective in the peri-operative management of carefully selected patients. The review appears to support the author's conclusion, but the limited search and poor reporting of the review methods, quality assessment and results data mean it is difficult to assess the reliability of these conclusions.

Authors' objectives
To evaluate the effects of cyclooxygenase (COX)-2 inhibitors in peri-operative settings.

Searching
PubMed was searched using the reported search terms. In addition, the reference lists of identified studies were screened.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Studies that evaluated COX-2 selective inhibitors were eligible for inclusion. The included studies evaluated celecoxib (200 mg), rofecoxib (25 mg, 50 mg or 1 mg/kg), valdecoxib (10 to 80 mg), parecoxib (20 to 40 mg) and ketorolac (30 mg). The drugs were administered orally and intravenously, and pre- and/or post-operatively. The studies evaluated single-dose and multiple-dose regimens. In some studies COX-2 inhibitors were given in combination with patient-controlled morphine sulphate. The control treatments included morphine sulphate (given via patient-controlled analgesia or intravenously), oxycodone, codeine, acetaminophen, nonselective non-steroidal anti-inflammatory drugs (NSAIDs; e.g. ibuprofen, diclofenac, indomethacin and naproxen), placebo, and combinations of these.

Participants included in the review
Studies of patients in peri-operative settings were eligible for inclusion. The included studies were in patients undergoing orthopaedic surgery, abdominal surgery, oral surgery and otolaryngologic surgery. The review also included studies of adult volunteers, normotensive salt-depleted patients and elderly patients (including those on normal and low sodium diets).

Outcomes assessed in the review
Studies that assessed post-operative analgesia, use of pre-emptive analgesia, platelet aggregation, bleeding time and renal function were eligible for inclusion. The review also assessed patient satisfaction, thromboxane beta2 levels, blood-pressure and adverse effects.

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

Assessment of study quality
The author stated that studies were assessed for sensitivity of the methods used to measure pain and statistical analysis, but provided no further details. The author did not state how the validity assessment was performed.
Data extraction
The author did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Where possible, for each study, the results were presented as text and the statistical significance of the reduction in total opioid dose was reported.

Methods of synthesis
How were the studies combined?
The studies were grouped by outcome and type of surgery and combined in a narrative.

How were differences between studies investigated?
Differences between the studies were discussed with respect to the comparator treatment.

Results of the review
Thirty RCTs were included. Twenty-two RCTs (n=4,105) were included in the assessment of pain-related measures. The number of patients in the other 8 RCTs was not reported.

Analgesic efficacy.

Orthopaedic surgery (9 studies, n=1,305).
All 6 studies that assessed opioid-sparing effects reported significant reductions (p<0.05) in opioid use in patients receiving selective COX-2 inhibitors. COX-2 inhibitors were associated with less use of rescue medication, lower pain scores and greater patient satisfaction compared with placebo (based on 4 studies).

Abdominal surgery (4 studies, n=571).
Three of 4 studies reported significantly lower pain scores in patients receiving COX-2 inhibitors (p<0.05), and 3 studies reported a significant reduction in total post-operative opioid dose.

Oral surgery (6 studies, n=1,991).
All 3 studies that compared selective COX-2 inhibitors with a non-selective NSAID reported comparable analgesic efficacy with these agents. All 3 studies reported a longer duration of action associated with COX-2 inhibitors. One study reported lower peak pain scores in patients who received rofecoxib compared with codeine plus acetaminophen.

Otolaryngologic surgery (3 studies, n=238). Three studies reported significantly lower pain scores associated with selective COX-2 inhibitors with or without acetaminophen compared with acetaminophen or placebo (p<0.05).

Platelet function (6 efficacy studies in surgical patients plus 3 studies in adult volunteers).
Three studies compared supratherapeutic doses of selective COX-2 inhibitors with standard doses of nonselective NSAIDs in volunteers. All 3 studies reported that COX-inhibitors had no effect on platelet function, but that nonselective NSAIDs were associated with significantly increased bleeding time and reduced platelet function. One study reported lower peak pain scores in patients who received rofecoxib associated with less platelet disturbance and intra-operative blood loss than diclofenac. Five efficacy studies that evaluated surgical blood loss reported no difference in blood loss with COX-2 inhibitors compared with opioid or placebo.

Renal function (4 studies).
One study reported a transient decrease in renal blood flow and glomerular filtration rate (GFR) associated with celecoxib in salt-depleted normotensive participants. One study reported a reduced GFR associated with rofecoxib and indomethacin in elderly patients. One study reported no difference in renal function between rofecoxib, celecoxib and
naproxen in elderly patients. One study reported a reduction in GFR associated with celecoxib and naproxen; the reduction with naproxen was significantly greater.

Authors' conclusions
Selective COX-2 inhibitors may be effectively used in the peri-operative management of carefully selected patients.

CRD commentary
The review question was clear with respect to the intervention, outcomes and study design. However, despite the stated eligibility of only peri-operative patients, studies of volunteers were also included; thus, the inclusion criteria were not adhered to. Limiting the search to one electronic database and reference lists of identified studies raised the possibility of publication bias. It was unclear whether any language restrictions had been applied, so the potential for language bias could not be assessed. The author stated that a limited assessment of validity was performed but results of this assessment were not reported, therefore the results from these studies and any synthesis might not be reliable. The methods used to select studies, assess validity and extract the data were not described, so it is not known whether any efforts were made to reduce reviewer errors and bias.

In view of the diversity of the studies, a narrative synthesis with studies grouped by type of surgery was appropriate. Results data were not reported for individual studies, which means it was not possible to verify the reported findings. In addition, not all studies were reported in the text. The review appears to support the author's conclusion, but the limited search, lack of reporting of review methods, inclusion of non peri-operative patients, lack of an assessment of study quality and lack of reporting of results data mean it is difficult to assess the reliability of these conclusions.

Implications of the review for practice and research
Practice: The author stated that, in view of the apparent decrease in function with selective COX-2 inhibitors, these drugs should be used cautiously in patients with pre-existing renal and cardiac disease. Research: The author stated the need for further research examining the effects of COX-2 inhibitors on peri-operative platelet function and surgical bleeding and renal function in peri-operative and surgical patients. There is also a need for RCTs in healthy patients to examine the effects of NSAIDs (as a class) on cardiovascular outcomes in order to determine in which subgroups of patients NSAIDs may be used safely.

Bibliographic details

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Subject indexing assigned by NLM

MeSH
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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.