Effect of preoperative Cox-II-selective NSAIDs (coxibs) on postoperative outcomes: a systematic review of randomized studies

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CRD summary
This review evaluated the effect of pre-operative cyclooxygenase-2 (Cox-2) inhibitors on post-operative pain, adverse events and other reported outcomes. Cox-2 inhibitors were found to have benefits in terms of reduced post-operative pain and analgesic consumption in comparison with placebo. Although the conservative conclusions reflect the evidence presented, poor reporting of the review methods makes it difficult to assess their reliability.

Authors' objectives
To evaluate the effect of using pre-operative cyclooxygenase-II-selective non-steroidal anti-inflammatory drugs (coxibs) on post-operative pain, adverse events and other reported outcomes.

Searching
PubMed and the Cochrane Library were searched up to August 2004, without any language restrictions. The reference lists of retrieved articles were checked, and companies marketing coxibs in the UK were contacted.

Study selection
Study designs of evaluations included in the review
Double-blinded, randomised controlled trials (RCTs) with active or placebo controls, and with at least 10 participants per group, were eligible for inclusion.

Specific interventions included in the review
Studies of coxibs were eligible for inclusion. The included studies evaluated rofecoxib, celecoxib, parecoxib and valdecoxib versus placebo, acetaminophen, naproxen sodium, diclofenac or ibuprofen as the comparator. A range of doses were administered depending on the specific drug being used. However, most of the studies administered either 25 or 50 mg rofecoxib, or 200 mg celecoxib.

Participants included in the review
Studies of adults undergoing any type of surgery were eligible for inclusion. The participants in the included studies underwent a range of surgical procedures: ear, nose and throat, dental, oral, orthopaedic, gynaecological, and general abdominal surgery. Patients received general, local, induction, or regional anaesthesia or sedation.

Outcomes assessed in the review
The studies had to report on post-operative pain or analgesic consumption, time for recovery, or adverse events to be included in the review. In addition, studies reported intra-operative blood loss, patient satisfaction, change in overall hospital stay, improved function, and cost-effectiveness.

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
Study quality was assessed using the Jadad scale. The studies had to score at least 2 out of the possible 5 to be included in the review. The 16-point Oxford Pain Validity Scale was also used; this assesses blinding, group size, outcome measures, baseline pain, internal sensitivity and data analysis. Study quality was assessed by at least two independent reviewers, and verified by a third. Any disagreements were settled by consensus.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.
For dichotomous outcomes, relative risks (RR) and 95% confidence intervals (CIs) were calculated for each study using an intention-to-treat analysis. For continuous variables, the mean difference was calculated.

**Methods of synthesis**

**How were the studies combined?**
The numbers of results favouring coxib, placebo or active comparator were calculated for each outcome using a vote counting system. The pooled RR and 95% CIs were calculated using a fixed-effect model. Numbers-needed-to-treat or to-harm were calculated when there was a statistically significant difference between the coxib and comparator. For continuous variables, the weighted mean difference (WMD) was calculated.

**How were differences between studies investigated?**
Heterogeneity was assessed visually using L’Abbe plots. Differences between the studies were discussed in the text. Sensitivity analyses were planned a priori to investigate blinding, study quality, validity and type of anaesthetic used. At least 3 studies had to be available in each category for pooling.

**Results of the review**

Twenty-two RCTs (n=2,246) were included in the review.

In terms of study quality, four scored 3, fourteen scored 4 and four scored 5 out of a possible 5 on the Jadad scale. The RCTs scored between 9 and 15 out of 16 on the Oxford Pain Validity Scale. Twenty-one of the RCTs were described as double blind.

Post-operative pain (20 RCTs): 7 of the 10 RCTs of major surgery and 9 of the 10 RCTs of minor surgery reported a statistically significant reduction in post-operative pain with coxibs relative to placebo.

Analgesic consumption (20 RCTs): 8 of the 11 RCTs of major surgery and 8 of the 9 RCTs of minor surgery reported a statistically significant reduction in post-operative analgesic consumption with coxibs relative to placebo. The WMD in post-operative analgesic use was 41% with rofecoxib, 32% with celecoxib and 21% with parecoxib.

Time to recovery (8 RCTs): only one RCT reported a statistically significant reduction in time to recovery with coxib relative to placebo.

Post-operative nausea and vomiting (17 RCTs): 4 trials reported a statistically significant reduction in post-operative nausea and vomiting with coxibs relative to placebo. When 4 trials were pooled, the RRxs revealed no statistically significant difference between coxibs and placebo for reducing nausea (RR 0.7, 95% CI: 0.5, 1.1), vomiting (RR 0.6, 95% CI: 0.3, 1.1), or nausea and vomiting (RR 0.9, 95% CI: 0.4, 2.0). When the results of 10 RCTs were pooled, the risk of any emetic event was not significantly lower with coxibs than with placebo (RR 0.8, 95% CI: 0.6, 1.1). Based on 5 RCTS, the use of post-operative anti-emetic was significantly reduced in participants taking coxibs relative to those taking placebo (RR 0.6, 95% CI: 0.5, 0.9). One RCT reported a reduction in anti-emetic use and better post-operative nausea control and vomiting with rofecoxib compared with diclofenac.

Adverse events: one study reported a patient developing a pulmonary embolism. All the other studies that mentioned adverse events reported only minor ones.

The results for the secondary outcomes (i.e. intra-operative blood loss, patient satisfaction, change in overall hospital stay and improved function) were reported.

**Cost information**

One RCT performed an economic analysis and reported a lower cost-effectiveness ratio for rofecoxib 50 mg ($3.6) than celecoxib 200 mg ($48.5) or paracetamol 2,000 mg ($47.4).

**Authors’ conclusions**

Pre-operative coxibs had benefits in terms of reduced post-operative pain, analgesic consumption and patient satisfaction in comparison with placebo. However, their effects on post-operative nausea and vomiting, recovery from surgery and economic benefit are still unclear.
CRD commentary
The research question was clear in terms of the intervention, study design and outcome. Only two electronic databases were searched, although this was without language restrictions and attempts were made to locate unpublished data. The authors did not investigate the possibility of publication bias. Study quality was assessed in duplicate. However, it was unclear whether similar methods were used to reduce error and bias during the study selection and data extraction stages of the review. Appropriate measures of effect were calculated. Although 17 trials reported on nausea and vomiting, only the results of 4 RCTs were used to produce the pooled estimate.

The potential for publication bias and the lack of detail regarding review methodology made it difficult to assess the reliability of the results. However, the authors drew conservative conclusions that seem to reflect the evidence presented.

The review included several trials which were subsequently retracted.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that large RCTs for different surgical procedures and different anaesthetic techniques are needed. Future studies should measure outcomes from surgery until the return to normal function, with long-term follow-up and economic analysis. The authors went on to state that studies need to discriminate between pre-operative coxibs alone and in combination with post-operative coxibs.

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