Reduction of opioid-related adverse events using opioid-sparing analgesia with COX-2 inhibitors lacks documentation: a systematic review

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CRD summary
This review evaluated opioid-related adverse events in studies of opioid sparing with cyclooxygenase-2 (COX-2) inhibitors compared with placebo in post-operative pain. The authors concluded that opioid sparing with COX-2 inhibitors does not have a clinically beneficial effect on opioid-related adverse events. The conclusion appears reliable based on the data presented, although relevant studies might not have been included.

Authors' objectives
To review opioid-related adverse events in studies of opioid-sparing post-operative pain treatment with cyclooxygenase-2 (COX-2) inhibitors.

Searching
MEDLINE (from 1966 to 2004), EMBASE (from 1989 to 2004) and the Cochrane Controlled Trials Register (2004) were searched for studies published in any language; the search terms were reported. The reference lists of retrieved reports and reviews were also checked. Abstracts and unpublished studies were not eligible for inclusion.

Study selection
Study designs of evaluations included in the review
Double-blind randomised controlled trials (RCTs) with at least 10 participants in each comparison group were eligible for inclusion.

Specific interventions included in the review
Studies of opioid-sparing analgesia using systemically administered COX-2 inhibitors, compared with placebo, were eligible for inclusion. The COX-2 inhibitors evaluated in the included studies were rofecoxib, celecoxib, parecoxib and valdecoxib. Details of the dosages used were given.

Participants included in the review
Studies of children or adults undergoing surgery and being administered post-operative pain relief were eligible for inclusion. The surgical procedures evaluated included dental extractions, hip and or knee replacements, coronary artery bypass, and otolaryngological and abdominal procedures. All of the included studies were performed in adult populations.

Outcomes assessed in the review
Studies that reported data on a significant reduction in the consumption of supplementary opioids with the COX-2 inhibitor and on opioid-related adverse events were eligible for inclusion. Adverse events considered eligible were incidence of nausea and vomiting, constipation, dizziness, sedation, pruritis and urinary retention 0 to 24 hours after surgery.

How were decisions on the relevance of primary studies made?
Two reviewers independently determined the eligibility of studies for inclusion. Any discrepancies were resolved by discussion.

Assessment of study quality
The authors assigned a quality score to each study (1 being the lowest and 5 the highest) using the Jadad instrument to assess randomisation, blinding and description of withdrawals. Two reviewers independently assessed the validity of the included studies. Any discrepancies were resolved by discussion.

Data extraction
One reviewer extracted the data using a standardised form, and a second reviewer checked them. Data on the occurrence of each adverse event of interest were extracted and used to calculate the relative risk (RR). Data were also extracted on the mean reduction in supplementary opioid demand 0 to 24 hours after surgery.

Methods of synthesis
How were the studies combined?
Data from the individual studies were combined using a fixed-effect meta-analysis. A pooled RR with 95% confidence intervals (CIs) was calculated separately for each adverse event. The number-needed-to-treat (NNT) was calculated, along with the 95% CI, to estimate the clinical relevance of adverse events for statistically significant pooled estimates using the weighted means of the experimental and control events’ rates.

How were differences between studies investigated?
The studies were tabulated and grouped according to adverse event. Characteristics of the included studies, such as the impact of painful operations and type of operation type, were considered in those studies that found a reduction compared with those that did not.

Results of the review
Nineteen studies (n=1,606), including 26 comparisons, were included in the review.

Overall, the included studies were of a high quality (median quality score 4 out of 5; range: 2 to 5).

Consumption of supplementary opioids (19 studies).
Supplementary opioid consumption (0 to 24 hours) was significantly reduced by an average of 35% (range: 14 to 100) with COX-2 inhibitors.

Opioid-related adverse events. No significant difference was found between COX-2 inhibitors and placebo for nausea (RR 1.04, 95% CI: 0.92, 1.18), vomiting (RR 0.91, 95% CI: 0.74, 1.12), constipation (RR 0.86, 95% CI: 0.67, 1.07), sedation (RR 0.94, 95% CI: 0.63, 1.41), pruritis (RR 0.84, 95% CI: 0.57, 1.24) or urinary retention (RR 1.20, 95% CI: 0.50, 2.91). The occurrence of dizziness was significantly higher in those treated with COX-2 inhibitors than those treated with placebo (RR 0.70, 95% CI: 0.50, 0.96). The corresponding NNT was 33 (95% CI: 17, 125).

Overall, the reporting of adverse events was poor.

Authors’ conclusions
The absence of high-quality data on adverse events in relevant trials means that the available data does not support the notion that opioid sparing with COX-2 inhibitors provides a clinically beneficial effect on opioid-related adverse events. Future trials need to use appropriate methods to report adverse events during the post-operative period.

CRD commentary
The review addressed a clear research question with inclusion criteria that appear appropriate. Several relevant databases were searched and an attempt was made to avoid language bias. However, only published studies were eligible, suggesting that some relevant studies might not have been included in the review. In addition, the authors only included studies that reported a significant reduction in the consumption of opioids, but did not define what was considered to be significant. Methods were used to minimise bias and error in the study selection, data abstraction and validity assessment processes. The validity of the individual studies was assessed and adequate details were presented on each included study.

Several characteristics of the included studies were considered in the analysis of the results, although no formal assessment of heterogeneity was undertaken. This makes it difficult to assess the appropriateness of the statistical combining of the studies. The authors considered the limitations associated with the quality and validity of reporting data on adverse events, and made appropriate recommendations for increasing the awareness and use of measuring and reporting adverse events in future trials.

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: Future studies need to promote and use appropriate methods for measuring and reporting adverse events in the post-operative period.

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