Effects of nonsteroidal antiinflammatory drugs on patient-controlled analgesia morphine side effects: meta-analysis of randomized controlled trials
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CRD summary
This review assessed the effects of non-steroidal anti-inflammatory drugs (NSAIDs) on morphine-related adverse effects in post-operative patient-controlled analgesia. The authors concluded that NSAIDs reduced post-operative nausea and vomiting and sedation, but not pruritus, urinary retention and respiratory depression. Other than the reporting of review methods, the review was well conducted and the authors’ conclusions are likely to be reliable.

Authors’ objectives
To assess the effects of non-steroidal anti-inflammatory drugs (NSAIDs) on morphine-related adverse effects in post-operative patients receiving patient-controlled analgesia (PCA).

Searching
PubMed and the Cochrane Controlled Trials Register were searched from 1966 to December 2003 using the reported search terms. Reference lists in published articles, reviews and correspondence were screened. Four named drug companies were contacted for additional unpublished studies. The review only included studies published in English.

Study selection
Study designs of evaluations included in the review
Double-blind randomised controlled trials (RCTs) that scored at least 3 on the Oxford validity scale (see Validity Assessment) and lasted at least 24 hours were eligible for inclusion.

Specific interventions included in the review
Studies that compared NSAIDs (either nonselective NSAIDs or selective cyclooxygenase-2 inhibitors) with placebo in patients receiving morphine PCA were eligible for inclusion. Studies were excluded if they used: a continuous morphine infusion or continuous regional analgesia in addition to PCA; only used a regional technique; used a non morphine opioid; used NSAID as a control; used another nonopioid analgesic in both groups; or used intrarectal NSAIDs. Most of the included studies compared intramuscular or intravenous NSAID with a placebo-control of intramuscular or intravenous saline; some studies used oral NSAIDs. The studies used a variety of different NSAIDs (ketorolac, tenoxicam, ketoprofen, parecoxib, dextroketoprofen, diclofenac, lysine acetyl salicylate, indomethacin, piroxicam, ibuprofen, naproxen and rofecoxib). The duration of treatment ranged from 24 to 72 hours.

Participants included in the review
Studies of adolescents (older than 12 years) or adults undergoing major surgery were eligible for inclusion. Studies of children (age younger than 12 years) or patients that required mechanical ventilation in the first 24 hours post-operatively were excluded. The included studies were in patients undergoing orthopaedic and pelvic or abdominal surgery.

Outcomes assessed in the review
Studies were included if they assessed morphine-related adverse effects such as nausea, vomiting, sedation, urinary retention, respiratory depression and patient satisfaction. The primary review outcome was nausea and/or vomiting in the post-operative setting. The review also assessed author-defined nausea, vomiting and any emetic event separately.

How were decisions on the relevance of primary studies made?
The authors did not state how studies were selected for the review, or how many reviewers performed the selection.
Assessment of study quality
The studies were assessed and scored using the 5-point Oxford validity scale, which considers randomisation, blinding and completeness of follow-up.

Two reviewers, not blinded to authors or results, independently assessed validity. Any disagreements were resolved by discussion, or with the aid of a third reviewer where required.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Some authors were contacted for additional information about the results. For dose-ranging studies, data were extracted from the highest dose NSAID group. For studies that did not report the use of intention-to-treat analysis, data were extracted on an intention-to-treat basis and used to calculate intention-to-treat results. Morphine requirements at 24, 36 and 48 hours were extracted.

Methods of synthesis
How were the studies combined?
Pooled relative risks (RRs) with 95% confidence intervals (CIs) were calculated using methods similar to the Mantel-Haenszel method; a random-effects model was used when significant heterogeneity was found. Where the results were statistically significant, the number-needed-to-treat (NNT) and 95% CI were calculated. A funnel plot and Egger's test were used to assess the potential for publication bias.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Q test. A sensitivity analysis (defined a priori) was used to explore the influence of type of surgery (peripheral versus pelvic or abdominal), intra-operative opioid and reversal of muscle relaxant on the results. The relationship between morphine consumption and the incidence of nausea and vomiting was examined using regression analysis, with weighting applied using the inverse of the variance.

Results of the review
Twenty-two RCTs (n=2,307) were included.

Post-operative nausea and vomiting (PONV).

NSAIDs significantly reduced PONV, post-operative vomiting and post-operative nausea. The RR was 0.704 (95% CI: 0.590, 0.841, P<0.001) for PONV, 0.678 (95% CI: 0.508, 0.906, P=0.008) for post-operative vomiting and 0.879 (95% CI: 0.785, 0.983, P=0.02) for post-operative nausea. The NNTs were 12 (95% CI: 9, 22), 15 (95% CI: 10, 51) and 16 (95% CI: 9, 108), respectively; no significant heterogeneity was found.

The decrease in morphine consumption was found to be linearly related to reductions in post-operative nausea (P=0.007) and post-operative vomiting (P=0.02).

NSAIDs significantly reduced PONV in patients undergoing orthopaedic surgery (RR 0.655, 95% CI: 0.467, 0.920) and pelvic or abdominal surgery (RR 0.684, 95% CI: 0.459, 1.020; P=0.06, borderline statistical significance). Neither the funnel plot nor Egger's test (P=0.49 for PONV) showed evidence of publication bias.

Sedation (10 studies).

NSAIDs significantly reduced post-operative sedation; the RR was 0.714 (95% CI: 0.537, 0.950, P=0.02) and the NNT was 27 (95% CI: 17, 154).

There was no significant difference between NSAIDs and control for pruritus (8 trials), urinary retention (7 trials) and respiratory depression (8 trials). The results were reported.
Authors' conclusions
NSAIDs reduced opioid-related adverse effects such as PONV and sedation, but not pruritus, urinary retention and respiratory depression.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Relevant reports were sought from several sources and attempts were made to locate unpublished studies. Limiting the included studies to publications in English might have resulted in the omission of some studies, and also raises the possibility of language bias. The authors used appropriate methods to assess publication and other potential sources of bias, and did acknowledge the potential for language bias. Methods were used to minimise errors and bias in the assessment of validity, but it was unclear whether similar steps were taken in the study selection and data extraction processes. The review only included RCTs meeting minimal specified validity criteria.

Adequate information on the included studies was reported. The studies were appropriately combined using meta-analysis, statistical heterogeneity was assessed, and the influence of various predefined factors on the results was examined. The review was limited by incomplete reporting of review methods. Other aspects of the review were well conducted and the authors' conclusions are likely to be reliable.

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

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