Paracetamol and NSAIDs for the reduction of morphine-related side effects after major surgery

Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs) for the reduction of morphine-related side effects after major surgery: a systematic review

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Executive summary

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Executive summary

Background

Patient-controlled analgesia (PCA) is a mainstay in the control of pain after major surgery. The drug most commonly used with PCA is morphine, but its administration can result in adverse effects, most commonly nausea and vomiting. Paracetamol (acetaminophen), non-steroidal anti-inflammatory drugs (NSAIDs) and cyclo-oxygenase 2 (COX-2) inhibitors are commonly used in conjunction with morphine following major surgery with the aim of reducing morphine consumption and the associated adverse effects. These non-opioids also have their own adverse effects. NSAIDs are associated with prolonged bleeding time and adverse gastrointestinal effects amongst other outcomes. The use of COX-2 inhibitors has been associated with increased thromboembolic events such as myocardial infarction and stroke, although these associations tend to be seen only with long-term use.

Objectives

To determine which class of non-opioid analgesics – paracetamol, NSAIDs or COX-2 inhibitors – is the most effective at reducing morphine consumption and associated adverse effects when used as part of multimodal analgesia following major surgery.

Methods

We conducted a systematic review of the effectiveness literature, which updated a previous review on this topic. MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched for the period January 2003 to February 2009. Published and unpublished studies were eligible and no language restrictions were applied. The reference lists of relevant systematic reviews were checked to identify relevant studies.

Two researchers independently screened studies for relevance based on the inclusion criteria, and disagreements were resolved by consensus or through discussion with a third member of the team. Randomised controlled trials comparing paracetamol, NSAIDs or COX-2 inhibitors to each other or placebo, in adults receiving PCA morphine following major surgery, were included. The COX-2 inhibitors rofecoxib and valdecoxib were excluded as these are no longer licensed in the UK. Only trials that reported 24-hour morphine consumption were included. The other outcomes of interest were morphine-related adverse effects (respiratory depression, nausea, vomiting, urinary retention, pruritus, dizziness and sedation) and adverse effects related to the non-opioids. The inclusion criteria differed slightly from the earlier review and the trials from this earlier review were screened for inclusion in the update.

Data were extracted by one researcher into a standardised form and checked by a second. A standardised scale was used to assess whether randomisation, concealment of allocation, double blinding, and the flow of patients within the trial were adequately described or not.

The main analysis was a mixed treatment comparison (MTC) evaluating the relative effects of the four treatment classes: paracetamol, NSAIDs, COX-2 inhibitors and placebo. Four main outcomes were prioritised for the analysis. These were 24-hour morphine consumption, sedation, nausea and vomiting, and surgical bleeding. The trials varied in how nausea and vomiting were recorded. To maximise the data available for the analysis, studies reporting nausea alone were pooled with studies reporting postoperative nausea and vomiting (PONV). Comparisons were described as statistically significant (at 5% level) when the credibility interval (CrI) did not cross 1 for odds ratio (OR) and zero for mean difference (MD). Trials making direct comparisons between the active interventions were also pooled in a meta-analysis using a random effects model. Sensitivity analyses were undertaken to explore the effect on 24-hour morphine consumption MTC results of study quality and classifying the treatments by individual drug rather than class of drug. In addition, a post hoc sensitivity analysis was undertaken to explore the effect of baseline

morphine consumption on the MTC analysis for 24-hour morphine consumption.

Results

Sixty relevant studies were identified, 40 were from the earlier review being updated and 20 were new studies. For morphine consumption, data were combined from 56 trials that randomised patients to four treatments, including placebo. When paracetamol, NSAIDs or COX-2 inhibitors were added to PCA morphine, there was a statistically significant reduction in morphine consumption: paracetamol (MD –6.34 mg; 95% CrI –9.02 to –3.65); NSAIDs (MD –10.18 mg; 95% CrI –11.65 to – 8.72); and COX-2 inhibitors (MD –10.92; 95% CrI –12.77 to –9.08). NSAIDs and COX-2 inhibitors were both significantly better than paracetamol, and there was no significant difference between NSAIDs and COX-2 inhibitors (MD –0.74; 95% CrI –3.03 to 1.56).

The sensitivity analyses for quality and baseline morphine consumption showed the results of the main analysis to be robust, though the results adjusted for baseline morphine consumption are probably a better estimate of the effect sizes. The analysis of individual drugs (as opposed to drug class) suggested that it was reasonable to group the drugs into three classes, though there appeared to be possible inconsistency across different NSAIDs.

Data were combined from 43 trials for nausea and PONV. There was a significant reduction in nausea and PONV with NSAIDs compared to placebo (OR 0.70; 95% CrI 0.53 to 0.88) but not for paracetamol or COX-2 inhibitors, nor for NSAIDs compared to paracetamol or COX-2 inhibitors.

Data were combined from 19 trials for sedation for all four treatments. There was no statistically significant difference between any intervention and comparator. Compared to placebo, there was a trend towards increased sedation with paracetamol (OR 1.62; 95% CrI 0.32 to 5.02) and decreased sedation with NSAIDs (OR 0.53; 95% CrI 0.20 to 1.01) and COX-2 inhibitors (OR 0.63; 95% CrI 0.18 to 1.49). Surgical bleeding was not reported in any paracetamol studies and in a single COX-2 inhibitor study. Based on six trials ($n = 695$), 2.4% of participants receiving an NSAID experienced surgery-related bleeding compared to 0.4% with placebo.

Conclusions

There was a decrease in 24-hour morphine consumption, compared to placebo, ranging from 6.3 mg to 10.9 mg, when paracetamol, NSAID or COX-2 inhibitors were added to PCA morphine following surgery. When the three drug classes were compared to each other the differences in morphine consumption were small and unlikely to be of clinical significance. In addition, the benefits in terms of reduction of morphine-related adverse effects do not strongly favour one of the three non-opioid analgesics.

Implications for health care

All three non-opioid analgesics were effective at reducing PCA morphine consumption in the first 24 hours following major surgery. NSAIDs and COX-2 inhibitors were more effective than paracetamol, but the differences were small and probably of limited clinical significance, especially when baseline morphine consumption is taken into consideration. The difference between NSAIDs and COX-2 inhibitors was marginal and not statistically significant. The adjusted results suggest a mean difference of less than 2 mg of morphine over 24 hours when any of the drug classes was compared to the others. In terms of morphine-related adverse effects, which is the more clinically relevant outcome, the results do not strongly favour one class of non-opioid analgesic: NSAIDs were ranked highest for reducing the primary morphine-related adverse effects but they were only marginally better than COX-2 inhibitors and paracetamol. Any morphine-sparing effects of these non-opioid analgesics need to be balanced against any adverse effects related to the analgesics themselves. There were a small number of surgical bleeding events, gastrointestinal bleeding and oliguria for participants treated with an NSAID.

Taking the evidence as a whole, the uncertainty suggested by the size of the probabilities of being most effective, the small reduction in morphine consumption and the wide confidence intervals for adverse effects outcomes, there does not appear to be a strong case for recommending routine addition of any of the three non-opioids to PCA morphine in the 24 hours immediately after surgery. In addition, there does not appear to be a strong case for favouring one drug class above the others.

Recommendations for research

Given the overlap in the effects of the three analgesics, there does not appear to be a compelling case for a further trial. However, any future trials testing new analgesics in conjunction with morphine, following surgery, should focus on morphine-related adverse effects, ensuring that the power calculation is based on key morphine-related adverse effects rather than morphine consumption. Also, there would be value in exploring whether taking baseline morphine consumption into account alters the results for morphine-related adverse effects.

Publication

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 08/114/01. The contractual start date was in February 2009. The draft report began editorial review in August 2009 and was accepted for publication in October 2009. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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