Effects of acetaminophen on morphine side-effects and consumption after major surgery: meta-analysis of randomized controlled trials
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CRD summary
The authors concluded that the addition of acetaminophen to intravenous patient-controlled analgesia with morphine reduces the need for morphine in patients undergoing major surgery, but does not affect morphine-related side-effects. The authors’ conclusions appear to be supported by the data presented, but limited reporting of review methods means it is not possible to confirm their reliability.

Authors’ objectives
To determine the effect of adding acetaminophen (paracetamol) to intravenous (i.v.) patient-controlled analgesia (PCA) with morphine on opioid-related side-effects in patients undergoing major surgery.

Searching
MEDLINE and the Cochrane Controlled Trials Register were searched from January 1966 to April 2003; the search terms were listed. Bibliographies of identified studies, review articles and correspondence were searched manually. Bristol-Myers-Squibb was contacted for additional data.

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 compared acetaminophen (oral or i.v.) with placebo, given in addition to PCA morphine, were eligible for inclusion. The exclusion criteria were: the use of continuous morphine infusion or continuous regional anaesthesia in addition to PCA morphine; the use of PCA with an alternative opioid (not morphine); the use of non-steroidal anti-inflammatory agents in the control group, or the use of other analgesics in either the intervention or the control group; and rectal administration of acetaminophen. Most of the included studies involved comparisons of i.v. acetaminophen and i.v. saline (placebo); other studies evaluated oral acetaminophen compared with placebo, PCA i.v. morphine plus acetaminophen compared with PCA i.v. morphine without placebo, and i.v. acetaminophen or propacetamol compared with placebo. Treatment began either during or after surgery and lasted between 24 and 48 hours.

Participants included in the review
Studies that included patients aged over 18 years who had undergone major surgery and required PCA morphine analgesia were eligible for inclusion. Most of the included studies were in patients undergoing orthopaedic surgery (including herniated disk surgery, spinal stabilisation, hip or knee arthroplasty, and acute limb fracture reduction and fixation); other studies were in patients undergoing elective hepatic resection and elective Caesarean section. No further details of the participants in the included studies were provided.

Outcomes assessed in the review
Studies that reported opioid-related side-effects (primarily nausea, vomiting) or patient satisfaction were eligible for inclusion. The primary outcome for analysis was post-operative nausea and/or vomiting (PONV). Other outcomes of interest were post-operative pain, sedation, pruritus, urinary retention, respiratory depression, and morphine use in first 24 hours. Definitions of each outcome were listed in the review. The included studies used different scales to measure post-operative pain, including visual analogue scales (VAS).

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
Two authors assessed the validity of the studies using the Oxford validity scale, which assesses the quality of the trial methodology as well as reporting. Any disagreements were resolved by discussion or by consensus with the third reviewer, where necessary. Trials scoring 3 or more points out of a maximum of 5 were eligible for inclusion.

Data extraction
The authors did not state how many reviewers performed the data extraction. Data from the original studies were reanalysed using an intention-to-treat analysis where possible. The level of statistical significance of treatment differences was presented for VAS pain scores after surgery and opioid consumption for each study.

Methods of synthesis
How were the studies combined?
Fixed-effect and random-effects (where statistical heterogeneity was found) models were used to calculate odds ratios for dichotomous variables and weighted mean differences (WMDs) for continuous variables, along with their 95% confidence intervals (CIs). For WMD calculations, the size of the study and standard deviation of morphine consumption in the individual studies were accounted for. Data from studies reporting VAS pain scores 24 hours after surgery were summarised in a l’Abbe plot and combined in a narrative.

How were differences between studies investigated?
Tests of statistical heterogeneity (chi-squared and I-squared) were conducted.

Results of the review
Seven RCTs (491 patients) were included in the review.

Acetaminophen administration did not affect the incidence of PONV (7 trials), sedation (6 trials), urinary retention (5 trials), pruritus (3 trials), respiratory depression (2 trials), or patient satisfaction (5 trials).

Four of the 6 studies reporting VAS pain scores reported no significant difference between treatments; the other 2 studies reported significant decreases in pain scores with the intervention. Based on 6 trials, acetaminophen administration was associated with significantly less use of morphine in the first 24 hours (WMD 9 mg, 95% CI: 3, 15, p=0.003). There was strong evidence of statistical heterogeneity (p=0.0002).

Authors’ conclusions
The addition of acetaminophen to PCA morphine reduced the need for morphine but did not affect the incidence of morphine-related side-effects.

CRD commentary
The review question and inclusion criteria were clearly described. The search strategy was thorough but might have omitted relevant unpublished data, which the authors acknowledged as a potential source of bias. The validity assessment was undertaken in duplicate, and the exclusion of studies with a low score was likely to have maximised the quality of the studies included in the review. There were no details of how studies were assessed for relevance or the data extracted, thus raising the potential for reviewer bias and error.

The methods used to pool the studies were appropriate. Heterogeneity was detected for morphine use, but the authors did not consider possible reasons for this; however, the forest plot showed that all studies had the same direction of treatment effect. The authors’ conclusions appear to be supported by the data presented, but limited reporting of review methods means it is not possible to confirm their reliability.

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

Research: The authors stated that more well-designed large-scale studies are needed to establish whether acetaminophen decreases morphine-related side-effects or not.

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