Perioperative single dose ketorolac to prevent postoperative pain: a meta-analysis of randomized trials
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CRD summary
The review concluded that single-dose ketorolac was effective to reduce post-operative pain as well as post-operative nausea and vomiting. However, interpretation of the data may have been limited by variation amongst studies and unclear study quality. The authors’ conclusions reflect the presented evidence but in light of the mentioned limitations their conclusions should be interpreted carefully.

Authors’ objectives
To evaluate the efficacy of single dose ketorolac to prevent post-operative pain.

Searching
PubMed, EMBASE and the Cochrane Database of Systematic Reviews were searched to 1st March 2011. Search terms were reported. The authors also searched the Internet using Google Scholar. No language restrictions were applied to the search. The authors searched reference lists of identified papers for additional studies.

Study selection
Only randomised clinical trials that compared a single peri-operative (pre-operative or intra-operative) dose of systemic ketorolac to an inactive control group who received placebo or no treatment were included. Participants had to be aged 18 years or older. Included studies had to report post-operative pain outcomes by pain scores or opioid consumption. Trials were excluded if they reported on analgesia after non-surgical or dental pain or if more than one dose of ketorolac was given peri-operatively. Studies were also excluded if they contained concurrent use of another analgesic regimen which did not allow direct comparison of ketorolac and placebo.

Four trials examined 30mg ketorolac, nine trials 60mg. A range of surgical procedures and types of anaesthesia were included. In most trials, ketorolac was administered pre-incision, the remaining trials used post-incision administration. All studies reported post-operative opioid consumption and/or pain scores.

Two independent reviewers selected studies for inclusion. Disagreements were resolved through discussion and, if necessary, through referral to a third reviewer.

Assessment of study quality
The quality of included trials was assessed by a modified Jadad 5-point quality scale evaluating randomisation, blinding, allocation concealment, and completeness of follow-up. The minimum score on the scale was 1, the maximum 5.

Two independent authors assessed study quality. Disagreements were resolved through discussion and, if necessary, through referral to a third reviewer.

Data extraction
Data were extracted for pain scores and opioid consumption and used to calculate mean differences and 95% confidence intervals (CIs). Pain scores were grouped as early (zero to four hours) or late (24 hours) acute post-operative pain scores at rest and movement and as cumulative opioid consumption (intravenous morphine equivalents) in the post-operative period. Visual analogue scale or numeric rating scales were converted to a 0 to 10 number rating scale. Postoperative opioid consumption was converted to equivalent dose of intravenous morphine. Data presented as median and range were converted to mean and standard deviation. Data were extracted on adverse events and used to calculate Peto odds ratio (OR) and 95% confidence intervals. Study authors were contacted for further information where required.

Methods of synthesis
Data were pooled and weighted mean differences (WMD) and 95% confidence intervals were calculated for continuous
data and Peto odds ratios were calculated for dichotomous data using a random-effects meta-analysis. Number-needed-to-treat (NNT) was calculated where appropriate. Funnel plots were examined using the Egger regression test to evaluate publication bias. Rosenthal's file-drawer analysis was performed where there was asymmetry in the funnel plot. The $I^2$ statistic was used to assess heterogeneity ($I^2$ above 30% was considered to indicate presence of heterogeneity). Subgroup analyses were conducted to investigate time and route of administration.

**Results of the review**

Thirteen trials (782 participants) were included. Some trials included more than one comparison. Sample sizes ranged from 20 to 126. The median score on the modified Jadad scale was 4.

**Early (zero to four hours) pain at rest**: Overall, ketorolac was associated with less early pain at rest than placebo (WMD -0.64, 95% CI -1.11 to -0.17, 14 comparisons). A dose of 30mg ketorolac was not associated with statistically significant less early pain at rest than placebo (three trials). A dose of 60mg ketorolac was associated with less early pain at rest (WMD -2.09, 95% CI -3.24 -0.95, 11 comparisons). There was evidence of high heterogeneity in this analysis ($I^2$=93%).

**Early (zero to four hours) pain at movement**: Both pre-incision (WMD -3.00, 95% CI -4.38 to -1.61) and post-incision (WMD -1.90, 95% CI -3.28 to -0.51) administration of 60mg ketorolac reduced early pain at movement (one trial). No trials investigated use of 30mg ketorolac.

**Late (24 hours) pain at rest**: Overall, ketorolac did not significantly reduce late pain at rest compared with placebo (eight trials). Neither 30mg (two trials) nor 60mg (six comparisons) ketorolac were associated with a statistically significant reduction of late pain at rest.

**Late (24 hours) pain at movement**: Neither pre- nor post-incision administration of 60mg ketorolac reduced late pain at movement (one trial). No trials investigated use of 30mg ketorolac.

**Post-operative opioid consumption**: Overall, ketorolac significantly reduced post-operative opioid consumption (WMD -1.73 milligrams, 95% CI -2.82 to -0.59, 14 comparisons). A dose of 30mg ketorolac did not significantly reduce post-operative opioid consumption (four comparisons). There was evidence of heterogeneity in this analysis ($I^2$=37%). A dose of 60mg ketorolac significantly reduced post-operative opioid consumption (WMD -1.64 milligrams, 95% CI -2.90 to -0.37) compared with placebo (10 comparisons). There was evidence of heterogeneity present in this analysis ($I^2$=71%).

**Post-operative nausea and vomiting**: Overall, ketorolac reduced post-operative nausea and vomiting compared with placebo (OR 0.57, 95% CI 0.36 to 0.88, NNT 12.5, 10 comparisons). A dose of 30mg ketorolac did not significantly reduce post-operative nausea and vomiting (three trials). But a dose of 60mg ketorolac did significantly reduce post-operative nausea and vomiting (OR 0.50, 95% CI 0.29 to 0.85, seven comparisons).

**Other Adverse events**: Most included trials did not report on adverse events. Ketalorac was associated with a significant increase in abnormal bleeding (OR 2.43, 95% CI 0.5 to 11, two trials). Ketalorac did not significantly increase post-operative gastritis symptoms (two trials).

There was no evidence of funnel plot asymmetry in these analyses. Other results were reported in the review.

**Authors' conclusions**

Overall, single-dose ketorolac was effective to reduce post-operative pain as well as post-operative nausea and vomiting. A dose of 60mg ketorolac offered significant benefits but evidence was insufficient to show significant benefits of the 30mg dose.

**CRD commentary**

The review question and inclusion criteria were clear. Several relevant sources were searched and the potential for language bias was low. There was risk of publication bias in the search as no unpublished studies were sought, but formal assessment of publication bias through inspection of funnel plots suggested that this risk was low. The use of independent, duplicate processes for study selection, data extraction and quality assessment reduced the risk of reviewer error and bias.
The method of synthesis was appropriate and suitable measures were used to assess heterogeneity. Only the composite score of the quality assessment was reported. This made it difficult to evaluate study quality in detail. High levels of heterogeneity in some analyses that could not be explained may limit the interpretation of the results. Most of the studies had small sample sizes. This may have affected the reliability of the results. Further, most included studies were published before 2000 which may have limited the generalisability of the results to current practice.

The authors’ conclusions reflect the presented evidence but in light of unclear study quality, small sample sizes and variation between studies their conclusions should be interpreted carefully.

Implications of the review for practice and research
Practice: The authors recommend anaesthesia providers reconsider the routine use of 30mg ketorolac given the paucity of the evidence.

Research: The authors state a need for large randomised trials as well as for trials focusing on the lower dose of 30mg ketorolac. Further, they suggest the conduct of trials that directly compared different routes of administration.

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