A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: the role of timing of analgesia
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Authors' objectives
To compare the efficacy of analgesia given either pre-operatively or intra- or post-operatively.

Searching
MEDLINE (from 1966 to 2000) and the Cochrane Library (2000) were searched; the search terms were reported. No language restrictions were applied. The reference lists of retrieved articles and review articles were also checked. Abstracts, correspondence and unpublished data were excluded.

Study selection
Study designs of evaluations included in the review
Double-blind, randomised controlled trials (RCTs) were eligible for inclusion. Trials of parallel and crossover designs were included. Trials with a sample size of less than 10 in each treatment group were excluded.

Specific interventions included in the review
Trials comparing analgesics given before versus after surgical incision were eligible for inclusion. The studies had to evaluate identical, or near identical analgesic regimens, with timing of administration of analgesia being the only difference between treatment arms. Studies reporting the use of other intra-operative analgesic treatments were also eligible for inclusion. Comparisons of pre-operative treatment with a placebo or non-treatment were excluded. Comparisons of pre-operative versus pre-operative plus post-operative treatment were also excluded. The treatments evaluated included non-steroidal anti-inflammatory drugs (NSAIDs) or paracetamol, opioids, methyl-D-aspartate (NMDA) receptor antagonists, epidural, caudal block, and wound infiltration or nerve block.

Participants included in the review
Patients undergoing any operative procedure were eligible for inclusion.

Outcomes assessed in the review
The primary outcome was post-operative pain relief. The outcome measures used were pain relief scores, time to first analgesic request, and consumption of supplementary analgesics.

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
Validity was assessed using the Jadad scale, with scores out of a maximum of 5 (see Other Publications of Related Interest no.1). The authors also noted the intensity of pain scores in each trial and whether the studies performed a power calculation. Two authors assessed validity independently, then reached a consensus.

Data extraction
Standard data collection sheets were used. The authors provided no further details about how the data were extracted for the review, or how many reviewers performed the data extraction. The mean visual analogue scale (VAS) pain scores were calculated for each trial from all available measurements made within 24 hours after surgery. Time to first analgesic request and demand for supplemental analgesic were extracted, together with reported P-values for statistical significance. Verbal rating pain scores and similar scores from five trials were converted to VAS pain scores.
Methods of synthesis
How were the studies combined?
The weighted mean differences (WMDs) in VAS pain scores were combined using either a fixed-effect (when statistically homogeneous) or a random-effects (when statistically heterogeneous) meta-analysis. The studies were weighted on the basis of study size and the standard deviation of the VAS scores in the individual trials. The studies were stratified according to type of analgesic, mode of administration and, where possible, surgical procedure. Data on analgesic consumption and time to first analgesic request were combined in a narrative.

How were differences between studies investigated?
The authors used L’Abbé plots (see Other Publications of Related Interest no.2) of VAS pain scores to investigate differences between the studies.

Results of the review
Eighty RCTs (n=3,761) were included.

NSAID or paracetamol (20 studies).
Of the 20 studies evaluating an NSAID or paracetamol, 14 showed no significant difference in effect of pre-emptive analgesia. Two RCTs, both using ketorolac (Jadad scores 2 and 5), reported a significant improvement in pain scores with pre-emptive analgesia (P<0.05). The pooled WMD of VAS scores was non significant (WMD 0 mm, 95% confidence interval, CI: -2, 2).

One RCT using diclofenac (Jadad score 4) reported that time to first analgesic request was improved by 1.5 hours, and the need for supplementary analgesia by 28%. Two RCTs, one using ketorolac and the other ketoprofen (Jadad scores 5 and 4, respectively) reported an improved time to first analgesic request, by 6 mg over 6 hours and 49 minutes, respectively.

Opioids (8 studies).
None of the studies reported significant differences in pain scores between patients receiving pre- or post-operative analgesia. When the WMDs of the VAS scores were pooled, the pain scores were significantly better in those receiving post-operative analgesia (WMD 5 mm, 95% CI: 1, 9).

NMDA receptor antagonists (8 studies).
One RCT using dextromethorphan (Jadad score 2) reported significantly improved pain scores in patients receiving pre-operative analgesia (P<0.05). There was no significant difference between patients receiving pre- or post-operative pain control in any of the other trials, or when the WMDs were pooled (WMD 2 mm, 95% CI: -8, 4).

Three RCTs, one using ketamine (Jadad score 4) and two using dextromethorphan (Jadad score 2 and 4) reported significantly reduced requirement for supplementary analgesia in patients receiving pre-operative pain control (P<0.05). One RCT (Jadad score 2) reported a significant increase in time to first request for analgesia in patients receiving pre-operative pain control (P<0.05).

Epidural (18 studies).

Single dose.

Three RCTs, one using fentanyl (Jadad score 4) and two using morphine (Jadad score 2), reported improvement in pain scores in patients receiving pre-operative pain control (P<0.05). The trial assessed pain at post-operative intervals. The one using fentanyl reported a significant difference only at 6 hours post-operatively, and the one using morphine only at 18 hours post-operatively. When the WMDs of the VAS scores were pooled, there was no significant difference between the treatment arms (WMD 4 mm, 95% CI: -9, 2).

Two RCTs, both using morphine (Jadad score 2), reported a significant increase in time to first analgesia request in
patients receiving pre-operative pain control (P<0.05). The requirement for supplementary analgesia was significantly lower in patients receiving pre-operative pain control in 7 RCTs: one using fentanyl, four morphine, one mepivacaine and one bupivacaine (P<0.05).

Continuous analgesia.

Three RCTs, one using morphine (Jadad score 2), one using mepivacaine (Jadad score 4) and one using bupivacaine (Jadad score 2), reported improvements in pain scores in patients receiving pre-operative pain control (P<0.05). When the WMDs of the VAS scores were pooled, there was no significant difference between the treatment arms (WMD 3 mm, 95% CI: -10, 5).

Only one RCT using morphine (Jadad score 2) reported time to first analgesia request; this was significantly increased in patients receiving pre-operative pain control (P<0.05). The same RCT reported a significantly lower requirement for supplementary analgesia in patients receiving pre-operative pain control (P<0.05).

Caudal block (6 studies).

Only one study using bupivacaine (Jadad score 2) reported a significant improvement in pain scores and a significantly reduced requirement for supplementary analgesia in patients receiving pre-operative pain control (P<0.05).

Wound infiltration or peripheral nerve block (20 studies).

Three RCTs using bupivacaine (Jadad scores 5, 4 and 4) reported significant improvements in pain scores in patients receiving pre-operative pain control (P<0.05). When the WMDs of the VAS scores were pooled, there was no significant difference between the treatment arms (WMD 0 mm, 95% CI: -3, 4).

Two RCTs, one using bupivacaine (Jadad score 5) and one using lidocaine (Jadad score 5), reported significant increases to time of first request for analgesia in patients receiving pre-operative pain control (P<0.05). Two RCTs, one using lidocaine (Jadad score 5), and the other bupivacaine (Jadad score 4), reported significant decreases in the requirement for supplementary analgesia in patients receiving pre-operative pain control (P<0.05).

**Authors' conclusions**

The authors' overall conclusion was negative with regard to the potential beneficial effect of pre-emptive analgesia on post-operative pain.

**CRD commentary**

The review question and inclusion criteria were clearly reported. The limited search and exclusion of unpublished data might have led to publication bias, and some studies might have been missed. The authors did not report details of how the study selection and data extraction processes were carried out, and it is therefore unclear whether attempts were made to minimise the introduction of error and bias. The authors combined clinically, and sometimes statistically, heterogeneous data in the meta-analyses. It might have been more appropriate for this data to be presented as a narrative synthesis. The authors' conservative conclusions and their recommendations for further research appear to follow from the evidence presented, and seem appropriate.

**Implications of the review for practice and research**

Practice: The authors did not state any implications for practice.

Research: The authors recommended that future studies should no longer investigate the role of timing of pre-emptive single-dose (short-lasting) analgesic treatment on the post-operative pain pattern. They suggested that future studies redirect their focus from the timing of peri-operative analgesia (pre-emptive analgesia) to protective analgesia aimed at the prevention of pain hypersensitivity (pathologic pain). They said that studies should investigate the effects of intensive and prolonged, multimodal analgesic (“protective”) interventions versus less aggressive, conventional peri-operative analgesia on immediate and late post-operative pain.
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