A qualitative systematic review of morphine treatment in children with postoperative pain

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CRD summary
The authors concluded that morphine alone was no more effective than other active interventions for relieving postoperative pain in children and caused more side effects. The conclusions may need to be interpreted with some caution, mainly due to limitations in the search, heterogeneity of the primary studies and the inclusion in the review of only morphine-related side effects.

Authors' objectives
To evaluate the efficacy and safety of different morphine regimens for children with postoperative pain.

Searching
MEDLINE via PubMed (from 1966), EMBASE (from 1989) and the Cochrane Central Register of Controlled Trials were searched to March 2006. Search terms were reported. The reference lists of articles retrieved were searched. Abstracts and unpublished articles were excluded. The search was not restricted by language, but articles in Japanese and Russian were excluded.

Study selection
Double-blinded randomised controlled trials (RCTs) were eligible provided they compared morphine with an active control or placebo for postoperative pain relief in children and had at least 10 participants in each study group. Outcomes of interest were efficacy (postoperative pain intensity, time to first postoperative analgesic request and need for rescue analgesia) and incidence of morphine-related side effects.

The review included studies of children aged from three months to 19 years who had undergone a wide range of surgical procedures. Morphine or control interventions were administered before, during or after surgery. Common routes and regimens for morphine were as follows: intravenous (IV) at 100 to 200 µg/kg, epidural at 30 to 100 µg/kg, intramuscular (IM) at 20 to 200 µg/kg and intrathecal at two to 20 µg/kg; all in single or multiple doses. Some studies used continuous infusions. Comparator interventions were administered by a variety of routes and were active (for example, ketamine, tramadol and bupivacaine) or inactive (saline and no treatment). Pain measures included validated pain scales and simple three to five point verbal/behaviour scales. Postoperative assessment periods varied from six to 72 hours. Studies restricted to patients with moderate or severe pain were excluded.

The authors stated neither how the papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
Study quality was evaluated using the Jadad scale, which measured adequacy of randomisation and blinding, and management of withdrawals and dropouts. Two authors independently assessed the adequacy of randomisation and blinding and reached consensus by discussion.

Data extraction
Data were extracted and indicated whether findings were statistically significant (p<0.05). Full results were reported only for significant findings (where available). Some data were extrapolated from diagrams. Data were extracted by one reviewer using standardised forms and checked by a second reviewer, with agreement reached by consensus. Study authors were not contacted for additional data.

Methods of synthesis
Results were combined in a narrative synthesis with accompanying evidence tables, grouped by morphine administration route and dose.
Results of the review
Thirty-six RCTs were included (n=1,908, sample size 20 to 120). Study quality was good, with a median Jadad score of 4 out of 5 (range 2 to 5).

Intravenous morphine (13 RCTs, 22 comparisons)

**Efficacy:** A significant benefit for morphine was seen for at least one outcome in all three comparisons that used an inactive control intervention, but in only one of 19 comparisons that used active controls.

**Side effects:** Nausea, vomiting and sedation were significantly more common with morphine in 10 of 22 comparisons.

Epidural morphine (12 RCTs, 14 comparisons)

**Efficacy:** A significant benefit for morphine was seen for at least one outcome in both comparisons that used an inactive control intervention, but in only two of 12 comparisons that used active controls.

**Side effects:** Nausea and/or vomiting, sedation, pruritus and/or respiratory depression were significantly more common with morphine in seven of 14 comparisons.

Intramuscular morphine (eight RCTs, nine comparisons)

**Efficacy:** A significant benefit for morphine was seen for at least one outcome in both comparisons that used an inactive control intervention, but in only two of seven comparisons with that used active controls.

**Side effects:** Vomiting was significantly more common with morphine in four of nine comparisons.

Intrathecal morphine (two RCTs, three comparisons)

**Efficacy:** A significant benefit for morphine was seen for at least one outcome for all three comparisons, all of which used an inactive control intervention. **Side effects:** No significant difference was found between the groups in the incidence of side effects.

No association between morphine dose and efficacy was noted.

Authors’ conclusions
Morphine alone was no more effective than other active interventions for relieving postoperative pain in children and caused more side effects compared with active controls.

CRD commentary
The review objectives and inclusion criteria were clear in most respects. However, it was unclear why the outcome of side effects applied only to morphine-related effects and did not appear to include other possible effects associated with comparator interventions. Relevant sources were searched for studies, but the restriction to published studies and the exclusion of some non-English studies meant that the review was prone to language and publication biases. Steps were taken to minimise the risk of error and bias in validity assessment and data extraction by having more than one reviewer make decisions independently, but it was unclear whether this also applied to study selection. Study validity was assessed, but the Jadad scale addressed only a limited range of criteria and no details were reported on individual studies, which made it difficult to be certain of the reliability of the evidence presented. The narrative synthesis grouped studies in a logical way and appropriately highlighted the differences between studies with active and inactive control interventions. The potential for bias created by clinical and methodological variation between the studies was highlighted in the text. The authors’ conclusions may need to be interpreted with some caution, mainly due to limitations in the search, heterogeneity of the primary studies and the inclusion in the review of only morphine-related side effects.

Implications of the review for practice and research
**Practice:** The authors stated that morphine alone was not necessarily the most suitable analgesic for postoperative pain...
in children, although in some clinical settings its first-line use may be justified by factors such as drug access, cost and familiarity.

**Research:** The authors stated that clinical trials that used standardised outcome measures with multimodal regimens for pain relief were needed, as were guidelines for evaluating paediatric medicines.

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