Benefit and risk of intrathecal morphine without local anaesthetic in patients undergoing major surgery: meta-analysis of randomized trials

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CRD summary
This review concluded that use of intrathecal morphine (injected into cerebrospinal fluid) decreased postoperative pain intensity and morphine consumption for patients undergoing major surgery under general anaesthetic. Respiratory depression remained a major safety concern. The authors' conclusions reflected the evidence and may be reliable, although the small sizes of included trials and variable trial quality should be borne in mind.

Authors' objectives
To assess the efficacy and safety of intrathecal (injected into the cerebrospinal fluid) morphine, without local anaesthetic, in patients undergoing surgery with general anaesthetic.

Searching
The following databases were searched for published studies up to November 2007 without language restriction: MEDLINE, EMBASE, and the Cochrane Library. Search terms were reported. Reference lists of retrieved publications were screened. Only studies published as full reports were eligible.

Study selection
Randomised controlled trials (RCTs) that compared a single intrathecal dose of morphine with controls (a placebo, a sham-injection or no treatment), in patients undergoing major surgery (abdominal, thoracic, orthopaedic or spinal) with general anaesthesia were eligible for inclusion. Eligible trials had to report pain outcomes or adverse effects. Trials with fewer than 10 patients per group were excluded. Trials evaluating morphine as an adjunct to intrathecal local anaesthetic were excluded, as were those assessing the combination of intrathecal opioids. The outcomes reported in the review included intraoperative fentanyl or sufentanil consumption, postoperative morphine consumption, postoperative pain intensity, and adverse events.

The patients in the majority of included trials underwent cardiac or abdominal surgery. Most trials administered intrathecal morphine before surgery; the doses ranged from 100µg to 4000µg. The majority of trials used morphine as a postoperative analgesic, administered either intravenously or through patient-controlled analgesia devices. The definitions of adverse events from the included trials were accepted. The included trials were published between 1985 and 2007.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
The quality of trials was assessed using the modified Oxford scale, a seven-point scale evaluating randomisation, concealment, blinding and drop-outs.

One reviewer performed the validity assessment and two reviewers independently checked the assessment, with any disagreement resolved by discussion with the fourth reviewer.

Data extraction
For continuous outcomes, means and standard deviations or standard errors were extracted to enable the calculation of mean differences and 95% confidence intervals (CIs). For dichotomous outcomes, event rates were extracted to enable the calculation of odds ratios (ORs) with 95% confidence intervals. The authors extrapolated 0 to 100mm visual analogue scales to a 0 to 10cm scale. The authors computed fentanyl equivalents of sufentanil doses by multiplying the average sufentanil doses by 10. The authors also dichotomised the pruritus data as the number of patients having any degree of pruritus. Trial authors were contacted for additional data.
One reviewer extracted the data and the other two reviewers independently checked the data extraction.

**Methods of synthesis**

The trials were combined in a meta-analysis. Weighted mean differences (WMDs) or Peto odds ratios, with 95% confidence intervals, were calculated. Statistical heterogeneity was assessed, but the authors did not state which statistic was used to assess the $p$ value. A fixed-effects model was used in the absence of significant heterogeneity. In the presence of significant heterogeneity, the dose-response effect was investigated using meta-regression; if there was no evidence of dose-response effect, a random-effects model was employed.

The numbers needed to harm (NNH), with 95% confidence intervals, were calculated. Subgroup analyses were performed on different types of surgery. Sensitivity analyses were performed to evaluate the impact of quality and year of publication of trials.

**Results of the review**

Twenty-seven RCTs were included in meta-analyses (n=1,205 patients). The median quality score of trials was 3 (ranging from 1 to 6).

Compared with controls, intrathecal morphine was associated with a significant reduction in intraoperative fentanyl or sufentanil consumption (WMD -145µg, 95% CI -181 to -109; nine RCTs) and postoperative 24 hours morphine consumption (WMD -16.9mg, 95% CI -23.7 to -10.1; 11 RCTs). Intrathecal morphine significantly reduced pain intensity at rest at four hours after surgery (WMD -1.9cm, 95% CI -2.9 to -0.8; five RCTs), at 12 hours after surgery (WMD -0.8cm, 95% CI -1.4 to -0.1; seven RCTs), and at 24 hours post surgery (WMD -1.0cm, 95% CI -1.7 to -0.4; eight RCTs). There were also significant reductions in pain intensity on movement at 12 hours after surgery (WMD -0.8cm, 95% CI -1.4 to -0.1; seven RCTs) and at 24 hours after surgery (WMD -1.0cm, 95% CI -1.7 to -0.4; eight RCTs). Intrathecal morphine was also associated with a significant reduction in the duration of hospital stay (WMD -0.49 day, 95% CI -0.89 to -0.09; eight RCTs).

Intrathecal morphine was associated with a significant increase in the incidence of respiratory depression (OR 7.86, 95% CI 1.54 to 40.3; NNH 84, 95% CI 47 to 409; 21 RCTs) and pruritus (OR 3.85, 95% CI 2.40 to 6.15; NNH 6, 95% CI 5 to 9; 18 RCTs).

Significant heterogeneity was only observed in the outcome of postoperative 24 hours morphine consumption ($p<0.001$), pruritus ($p=0.04$), and all the outcomes of postoperative pain intensity ($p$ values not reported).

Subgroup analyses showed a significantly higher reduction in postoperative 24 hours morphine consumption after abdominal surgery, compared with after cardiac-thoracic surgery.

Sensitivity analyses did not materially affect the results. There was no evidence of a dose-response effect.

**Authors' conclusions**

The use of intrathecal morphine decreased postoperative pain intensity and morphine-consumption for patients undergoing major surgery under general anaesthetic. The reduction in postoperative morphine consumption was more pronounced after abdominal surgery than after cardiothoracic surgery. Respiratory depression remained a major safety concern.

**CRD commentary**

The inclusion criteria of the review were clear. Relevant databases were searched. Efforts were made to find published studies, but not unpublished studies, which introduced the potential for publication bias. There was no language restriction in the search, which minimised the risk of language bias. Steps were taken to minimise errors and biases by having more than one reviewer independently performed the validity assessment and data extraction, but it was unclear whether study selection was also performed in duplicate.

Relevant criteria were used to examine the trial quality. Statistical heterogeneity was assessed and appropriate methods
were used to pool the results.

The authors' conclusions may be reliable, although the small sizes of the included trials and variable trial quality should be borne in mind.

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

**Practice**: The authors stated that the usefulness of intrathecal morphine in patients undergoing cardiothoracic surgery should be questioned; it may be appropriate to abandon this analgesic intervention. Clinicians should be aware that the optimal dose (i.e. with adequate analgesic efficacy but without life-threatening respiratory depression) of intrathecal morphine remains unknown.

**Research**: The authors stated that further research is required to quantify the benefits and risks of very low doses of intrathecal morphine in patients undergoing abdominal surgery.

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