Risks and side-effects of intrathecal morphine combined with spinal anaesthesia: a meta-analysis

Gehling M, Tryba M

CRD summary
This review found the use of intrathecal morphine in combination with spinal anaesthesia for post-operative analgesia was associated with an increase in nausea, vomiting and pruritus. The authors' conclusions reflected the evidence presented but some methodological weaknesses mean that the reliability of these conclusions is unclear.

Authors’ objectives
To assess the frequency of side-effects in patients receiving intrathecal morphine in combination with spinal anaesthesia.

Searching
MEDLINE was searched from inception to 2007; search terms were reported. Reference lists of retrieved articles were also searched for additional studies. It was unclear if any language restrictions were imposed. Study authors were not contacted to provide unpublished data.

Study selection
Randomised controlled trials (RCTs) investigating the use of intrathecal morphine in combination with spinal anaesthesia as a primary intervention in post-operative patients compared with a placebo were eligible for inclusion. Trials of general anaesthesia were excluded.

The participants in the included trials were undergoing surgery for: caesarean sections; orthopaedic surgery including knee and hip replacements; gynaecological reasons including tubal ligation; arthroscopy; transurethral prostatectomy; and haemorrhoids. Intrathecal morphine was administered at a range of doses from 0.025mg to 2.5mg. Some patients in the placebo groups received systemic opioids. The primary end-points were the frequencies of nausea, vomiting, pruritus, urinary retention and respiratory depression.

The authors did not state how the papers were selected for review, or how many reviewers performed the selection.

Assessment of study quality
Methodological quality was assessed using the recommendations of McQuay and Moore, a method scored on a 1 to 5 scale derived using appraisals of randomisation, blinding and withdrawals. A score of 5 points indicated a high quality trial.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
Two reviewers extracted data independently to permit the calculation of relative risks (RR) and 95% confidence intervals (CI) for nausea, vomiting, pruritus and urinary retention (which was recorded if patients had a urinary catheter placed because of retention or other urinary problem). Respiratory depression was derived from data on patients with a respiratory rate of less than either 12, 10 or eight breaths per minute. For respiratory depression, the risk differences (RD) between placebo and intrathecal morphine were calculated.

Methods of synthesis
The pooled relative risks and 95% confidence intervals for nausea, vomiting, pruritus and urinary retention were calculated using a fixed-effect model, as were the pooled risk differences and 95% confidence intervals for respiratory depression. The Cochran’s Q statistic and I² tests were used to evaluate heterogeneity across the trials. Sub-group analyses were also performed on the basis of dose of morphine and the quality of the included trials.
Results of the review
Twenty-eight studies (n=1,314 patients) were included in the review. In the assessment of methodological quality, 25 trials (89%) recorded a score of 3 or higher, with six trials recording the highest quality score of 5 points. A total of 790 patients received intrathecal morphine and 524 patients received a placebo.

There were statistically significant increases in the following outcomes observed with the use of intrathecal morphine: nausea (RR 1.3, 95% CI 1.1 to 1.5; 24 RCTs), vomiting (RR 1.6, 95% CI 1.1 to 2.2; 19 RCTs) and pruritus (RR 2.0, 95% CI 1.6 to 2.4; 25 RCTs). There were no statistically significant changes in urinary retention or respiratory depression after treatment with intrathecal morphine.

Lower doses of less than 0.3mg of intrathecal morphine were associated with increased incidences of vomiting (RR <0.3mg 3.1, 95% CI 1.5 to 6.4) compared with trials in which 0.3mg or more of morphine were used (RR ≥0.3mg 1.3, 95% CI 0.9 to 1.9). Conversely, higher doses of 0.3mg or more intrathecal morphine were found to increase the incidence of pruritus (RR ≥0.3mg 5.0, 95% CI 2.9 to 8.6) compared with doses lower than 0.3mg (RR <0.3mg 1.8, 95% CI 1.4 to 2.2). There were no differences observed between the dosing groups for the outcomes of nausea and urinary retention. The incidence of respiratory depression in patients treated with less than 0.3mg of intrathecal morphine was two out of 247 (1%) patients, compared with seven out of 80 (9%) patients when given a dose of 0.3mg or more.

Increased relative risks of nausea (RR 3.4, 95% CI 1.7 to 6.6) and vomiting (RR 2.5, 95% CI 0.9 to 6.6) were found in the trials with a quality assessment method quality score of 4 points, but not in trials with a method quality score of 5 point. The relative risk of pruritus increased as the method scores increased, although the highest relative risk was calculated in the two trials with a method quality score of 2 points (RR 11.5, 95% CI 1.6 to 83.1). No association was found between the incidence of urinary retention or the risk of respiratory depression and the method quality scores of the trials.

There was no statistically significant heterogeneity reported in any of the analyses of the pooled results for the outcomes examined.

Authors' conclusions
The use of intrathecal morphine was associated with a moderate and clinically relevant increase in nausea, vomiting, pruritus and urinary retention. Higher doses of intrathecal morphine were also associated with more episodes of respiratory depression.

CRD commentary
The review addressed a clear question that was broad in scope. The literature search was limited, and appeared to be confined only to published studies; there was no attempt to identify unpublished or grey literature. It was also unclear if any language restrictions were imposed. Consequently, relevant studies may have been missed and language and publication biases could not be ruled out. Steps were taken to minimise reviewer bias and errors in data extraction, but not explicitly reported for study selection and the validity assessment.

The authors stated there was some heterogeneity in the incidence of side-effects in the included trials, possibly due to differences in the documentation and reporting of side-effects. There was little statistical heterogeneity in the pooled results, so the authors’ decision to combine the results in a meta-analysis was appropriate. The quality of the majority of the included trials ranged from fair to high quality.

The authors’ conclusions regarding the incidence of adverse events reflected the results of review, although their conclusions about the results for urinary retention were based only on a dose-dependent trend. However, the limited literature search, potential language and publication biases, and the lack of information on the conduct of some parts of the review mean that the reliability of the authors' conclusions is unclear.

Implications of the review for practice and research
Practice: The authors stated that prophylaxis and therapy for side-effects will be required if spinal anaesthesia is to be supplemented by intrathecal morphine. In addition, continuous monitoring or observation of the respiratory function of
patients is also necessary. Requirements will be similar for patients receiving systemic opioids. There is no evidence to support the extended monitoring of patients who receive low-dose intrathecal morphine.

**Research:** The authors did not state any implications for research.

**Funding**
Not stated

**Bibliographic details**

**PubMedID**
19462494

**DOI**
10.1111/j.1365-2044.2008.05817.x

**Original Paper URL**
http://onlinelibrary.wiley.com/journal/122295137/abstract

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Analgesics, Opioid /administration & dosage /adverse effects; Anesthesia, Spinal; Female; Humans; Injections, Spinal; Male; Morphine /administration & dosage /adverse effects; Pain, Postoperative /prevention & control; Postoperative Complications /chemically induced; Postoperative Nausea and Vomiting /chemically induced; Pruritus /chemically induced; Randomized Controlled Trials as Topic; Respiratory Insufficiency /chemically induced; Urinary Retention /chemically induced

**AccessionNumber**
12009106068

**Date bibliographic record published**
23/09/2009

**Date abstract record published**
24/03/2010

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.