Intraoperative and postoperative analgesic efficacy and adverse effects of intrathecal opioids in patients undergoing Cesarean section with spinal anaesthesia: a qualitative and quantitative systematic review of randomized controlled trials


Authors' objectives
To investigate the effect of intrathecal opioids added to spinal anaesthesia on intra-operative and post-operative pain, and to evaluate adverse effects in patients scheduled for Caesarean section.

Searching
MEDLINE was searched from 1966 to 1998, The Cochrane Library from 1998, and EMBASE from 1981 TO 1998, without any restrictions on publication language. Different search strategies were used with freetext combinations including the following keywords: 'spinal', 'subarachnoid', 'intrathecal', 'opioid', 'anaesthesia', 'local anaesthesia', 'postoperative analgesia' and 'cesarean section'. The final search was conducted on July 15, 1998. References from retrieved reports and review articles were also examined. Abstracts and unpublished observational data were excluded.

Study selection
Study designs of evaluations included in the review
Blinded randomised controlled trials (RCTs) were eligible.

Specific interventions included in the review
Comparisons of the addition to spinal anaesthesia of a single intrathecal dose of opioid versus placebo (e.g. saline) or no treatment were eligible. Local anaesthetic agents included bupivacaine (9.1 to 22.5 mg), tetracaine (10 mg) and lidocaine (80 mg). Opioids included morphine (0.05 to 0.25 mg), fentanyl (2.5 to 60 microg), sufentanil (2.5 to 20 microg), and buprenorphine (0.03 to 0.45 mg).

Participants included in the review
Patients undergoing Caesarean section using spinal anaesthesia were eligible.

Outcomes assessed in the review
Only studies reporting post-operative pain were eligible. Post-operative pain was evaluated by the consumption of supplemental analgesics, and the number of patients not needing supplemental analgesics intra-operatively. The following side-effects were also assessed: pruritus, nausea, vomiting, and respiratory depression. Respiratory depression was defined as a respiratory rate of less than 10 breaths per minute.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
Validity was assessed and scored using the 3-item (randomisation, blinding and reporting of drop-outs), 5-point scale of Jadad et al. (see Other Publications of Related Interest). Three of the authors independently read and scored each report meeting the inclusion criteria.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. The following data were extracted: patients, type and dose of local anaesthetic, opioid used for spinal anaesthesia and analgesia, study end points, adverse effects and observation periods. For the quantitative analysis,
weight normalised doses of fentanyl were recalculated to total dose based on the demographic data in one study.

Methods of synthesis
How were the studies combined?
The weighted number of patients not needing supplemental intra-operative analgesia (NNT) and number-needed-to-harm (NNH) for each of the 4 side-effects (pruritus, nausea, vomiting and respiratory depression) were calculated together with the respective 95% confidence intervals (CIs) using a fixed-effect model. Data from control patients in studies investigating more than one opioid or dose were included in more than one analysis, but control data were not counted more than once for the combined analysis.

Data on post-operative pain scores and supplemental analgesics were combined qualitatively.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

Results of the review
Fifteen RCTs (816 patients) were included.

Four different opioids were given to 535 patients in 32 treatment arms and 23 different doses; 281 patients acted as controls. The quality scores ranged from 2 to 5 (median = 3).

Post-operative pain scores (4 RCTs). 1. Morphine (3 RCTs): morphine decreased pain scores for 24 hours post-operatively in 2 RCTs (1 RCT included 2 different doses of morphine), and prolonged pain relief in 1 RCT compared to control.

2. Fentanyl (2 RCTs): no effect for fentanyl was found on pain scores during 24 hours post-operatively.

Time to first administration of supplemental analgesic post-operatively (12 RCTs).

Criteria for the outcome were defined in 10 RCTs.

The median time to first analgesic with local anaesthetic alone was 2 hours (range: 1 - 4 hours) in 10 studies with bupivacaine, and 1 hour and 8 hours in 2 studies with lidocaine and tetracaine, respectively.

1. Morphine (4 RCTs with 6 treatment arms and 3 doses): median time to first analgesic was 27 hours (range: 11 - 29 hours). Morphine at doses of 0.1 and 0.2 mg decreased time to first administration in all 5 comparisons reporting this outcome. A dose of 0.05 mg had no significant effect in 1 comparison.

2. Fentanyl (7 RCTs with 15 treatment arms and 12 doses): reporting of outcomes was limited to one of 7 doses in 1 RCT. Results were inconsistent.

3. Buprenorphine (1 RCT used 2 different doses) and sufentanil (2 RCTs with 5 doses): both drugs increased the time to first administration with all doses.

Consumption of post-operative supplemental analgesics (11 RCTs).

1. Morphine (5 RCTs with 7 treatment arms and 3 doses): morphine at doses of 0.05, 0.1 and 0.2 mg decreased consumption of supplemental analgesic from 0 to 24 hours post-operatively in all comparisons.

2. Fentanyl (6 RCTs with 14 treatment arms and 12 doses): results were inconsistent, with 5 RCTs reporting no effect on consumption with fentanyl compared to control, and 1 RCT reporting decreased consumption.

3. Sufentanil (1 RCT and 2 doses): consumption of supplemental analgesic was reduced from 0 to 6 hours, but not from 6 to 24 hours, post-operatively.
Number of patients not needing supplemental analgesic intra-operatively (13 RCTs, with 739 patients, including 485 receiving opioids and 254 controls): results were inconsistent with 10 of the 28 comparisons showing a significantly-reduced need for intra-operative analgesic, compared to control. The pooled results from all opioids and doses was 96% for patients not requiring supplemental analgesic for opioid treatment, compared to 76% for control. Median NNT was 4.9 (range: 3.9 - 6.9).

Adverse effects (12 RCTs).

Observation periods ranged from 0 to 24 hours in 9 RCTs, and until first narcotic administration, 0 to 12 hours, and 0 to 48 hours post-operatively in 3 RCTs.

1. All opioids.

Nausea (11 RCTs) and vomiting (8 RCTs) were significantly more common with any intrathecal opioid than with control; NNH were 9.7 (95% CI: 6.2, 21.5) and 14.5 (95% CI: 8.1, 70.9), respectively.

Respiratory depression (12 RCTs): pooled NNH for all opioids and all doses was not significantly different for all opioids, compared to control.

Pruritus (11 RCTs): pruritus was significantly more common with opioids treatment. Pooled NNH was 2.3 (95% CI: 1.1, 1.9).

2. Morphine: pruritus (6 RCTs), NNH 2.6 (95% CI: 2.1, 3.3); nausea (5 RCTs), NNH 6.3 (95% CI: 4.2, 12.5); vomiting (6 RCTs), NNH 10.1 (95% CI: 5.7, 41.0).

3. Fentanyl: pruritus (3 RCTs), NNH 2.2 (95% CI: 1.8, 2.7); nausea (4 RCTs), NNH 21.9 (95% CI: 8.0, infinity); vomiting (2 RCTs), NNH 43.3 (95% CI: 11.4, infinity).

4. Data for buprenorphine and sufentanil were based on few studies. Buprenorphine (1 RCT with 45 patients, including 30 receiving opioids and 15 controls): pruritus, NNH 10.0 (95% CI: 4.8, infinity); nausea, NNH 4.3 (95% CI: 2.3, 38.0); vomiting, NNH 6.0 (95% CI: 2.7, infinity).

Sufentanil (2 RCTs with 77 patients, including 67 receiving opioids and 10 controls): pruritus, NNH 1.4 (95% CI: 1.1, 1.9); nausea, NNH 4.3 (95% CI: 2.0, infinity).

Univariate logistic regression showed the relative risk of post-operative pruritus increased with increasing doses of morphine (p<0.00001), fentanyl (p<0.002) and sufentanil (p<0.002). Increasing the dose of morphine also increased the relative risk of post-operative nausea (p<0.0001) and vomiting (p<0.006).

Authors' conclusions

Intrathecal morphine produced a clinically-relevant reduction in post-operative pain and analgesic consumption. However, there is only evidence for a small effect with fentanyl and sufentanil. The relative risk of both pruritus and nausea or vomiting increased in a dose-dependent manner with morphine. Based on current evidence, the authors recommend 0.1 mg morphine as the drug and dose of choice. For every 100 women receiving 0.1 mg intrathecal morphine added to spinal anaesthesia, 43 patients will experience pruritus, 10 will experience nausea and 12 will experience vomiting post-operatively, all of whom would not have experienced these adverse effects without treatment.

CRD commentary

The aims were stated and the inclusion criteria were defined in terms of the study design, participants, intervention, and outcomes. Several relevant databases were searched and no language restrictions were applied. Unpublished material was excluded, raising the possibility of publication bias. The methods used to select the studies were not described. The included studies were limited to blinded RCTs, validity was assessed and scored using defined criteria, and methods used to score validity were reported. Relevant data were presented in tabular format, although methods used to extract the data were not described. Statistical heterogeneity was not assessed and the data were pooled. Where differences in
results were reported, potential reasons for this heterogeneity were not discussed.

The evidence supports the authors’ conclusion.

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

Practice: The authors recommend 0.1 mg morphine as the drug and dose of choice. For every 100 women receiving 0.1 mg intrathecal morphine added to spinal anaesthesia, 43 patients will experience pruritus, 10 will experience nausea and 12 will experience vomiting post-operatively.

Research: The authors did not state any research implications of the review.

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