Analgesic efficacy and adverse effects of epidural morphine compared to parenteral opioids after elective caesarean section: a systematic review

Bonnet MP, Mignon A, Mazoit JX, Ozier Y, Marret E

CRD summary
The authors concluded that epidural morphine after caesarean section increased the time to first request for a rescue analgesic (limited to the first postoperative day) and decreased pain postoperatively, but increased the risks of nausea and pruritus. Apart from some limitations in reporting of the review process, the authors’ conclusions reflect the reasonable quality evidence presented and seem reliable.

Authors' objectives
To evaluate the analgesic effectiveness and side effects of epidural morphine compared with parenteral opioids following elective caesarean section.

Searching
PubMed, EMBASE, and Cochrane Central Reigster of Controlled Trials (CENTRAL) were searched for studies published between 1966 and 2009. Search terms were reported. References lists of relevant articles, reviews and other correspondence were searched to locate additional studies.

Study selection
Randomised controlled trials (RCTs) that compared epidural morphine (administered in a single dose) with systemic opioids (given systematically or on demand) in women after elective caesarean section were eligible for inclusion. Epidural morphine could be administered during or after surgery. Trials reporting per protocol analysis of less than 80% of patients were excluded.

The primary outcome of interest was time from drug injection until the first request for a rescue analgesic. Eligible secondary outcomes were: morphine consumption during the first postoperative day; pain scores at six, 12, and 24 hours after surgery; incidence of morphine-related adverse effects; postoperative nausea and/or vomiting; and respiratory depression.

Just under half of included trials used a placebo comparator. Various morphine doses (from 1mg to 8mg), administration methods, and timing of intervention and comparator were used; a range of supplementary local anaesthetics were included.

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

Assessment of study quality
Trial quality was assessed using a modified version of the Jadad scale covering randomisation, allocation concealment, double-blinding and follow-up. The modified version allowed a maximum score of 7 points.

Two reviewers independently carried out the quality assessment. Disagreements were resolved by consensus involving a third independent reviewer.

Data extraction
Data were extracted on mean time and range relating to the first request for rescue analgesic, and to enable the calculation of relative risks (RR) and 95% confidence intervals (CI) for adverse events. Also extracted was morphine consumption (mg) during the first postoperative day, and data on visual analogue scale (VAS) scores for pain.

The authors did not state how many reviewers carried out the data extraction.
Methods of synthesis
Data were pooled in a meta-analysis, using a random-effects model in the presence of statistical heterogeneity. Linear regression was applied to study the relationship between morphine consumption during the first postoperative 24 hours and epidural morphine dose. Correlations between epidural morphine dose and side effects were assessed using Kendall test of agreement. L'Abbe plots were used to evaluate VAS scores of pain relief over time, and to assess statistical heterogeneity across the trials. Where data were available, the Emax model (the maximum theoretical time until first request for a rescue analgesic) was used to evaluate the relationship between epidural morphine dose and time to first request for rescue analgesic.

Results of the review
Ten RCTs were included in the meta-analysis (n=442 women). Four trials compared epidural morphine with placebo, and six compared epidural morphine with parenteral morphine. The median quality score was 4 points (range 2 to 5).

The pooled analysis of six trials revealed a mean time to request for a rescue analgesic after caesarean section in the epidural morphine group was 19 hours (range 5.4 to 29.2) compared with 3.4 hours (range 2.0 to 4.4) in the parenteral opioid group (Emax 29.7 hours, 95% CI 25.2 to 33.9). Increasing the dose of epidural morphine corresponded with an increase in time to request, but with a ceiling effect at 30 hours.

There was a statistically significant linear relationship between epidural morphine dose and rescue parenteral morphine request during the first 24 hour postoperative period (five trials). VAS scores were lower for epidural morphine in all five trials reporting data (four trials at six hours; two trials at 12 hours; and one trial at 24 hours).

Statistically significant adverse effects relating to epidural morphine at doses between 2mg and 8mg were reported for postoperative nausea (RR 1.95, 95% CI 1.17 to 3.26; six trials) and pruritus (RR 2.71, 95% CI 2.05 to 3.58; nine trials).

Authors' conclusions
Compared with parenteral opioids, epidural morphine after caesarean section increased the time to first request for a rescue analgesic; a dose-effect relationship was evident with a ceiling limited to the first postoperative day. Epidural morphine also decreased pain at six and 12 hours postoperatively, but increased the risks of nausea and pruritus.

CRD commentary
This review addressed a clear question, and presented potentially replicable inclusion criteria. The search strategy, whilst accessing relevant sources, was limited to published studies and therefore carried a risk of publication bias. Methods to minimise reviewer error and bias were evident in the process of quality assessment, but not for study selection or data extraction.

Trial quality assessment was carried out using appropriate criteria; the results showed that included trials were of a reasonable standard. Trial details were presented, and clinical heterogeneity was evident. The chosen method of synthesis appeared to be appropriate in light of possible statistical heterogeneity, which was reported to be assessed but not clearly presented. Apart from some limitations in reporting of the review process, this review was based on reasonable quality studies and the authors’ conclusions seem reliable.

Implications of the review for practice and research
Practice: The authors stated that it is reasonable to recommend an epidural morphine dose of 4mg to facilitate effective pain relief after caesarean section.

Research: The authors stated that large randomised controlled trials are needed to evaluate the relationship between epidural morphine dose and incidence of opioid side effects.

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